International Workshop on Risk Assessment and Good Epidemiological Practices

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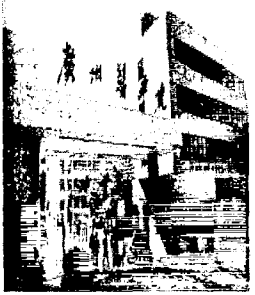

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July 14-17, 1997
Guangzhou, People's Republic of China

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International Workshop on Risk Assessment and Good Epidemiological Practices

July 14-17, 1997, Dong Fang Hotel, Guangzhou, China

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1. Goals:

The three day workshop aims to provide a forum for exchange of ideas and viewpoints between applied and basic research scientists, with respect to methods of analysis in chronic disease epidemiology, including:

(1) methodologic issues on personal exposure measurement to hypothesized risk factors in the environment, e.g., complex air pollutants categorized as low level, long-range emission types;

(2) exposure assessment for low dose and low risk environmental agents in cases in which classical epidemiologic tools may be insufficient;

(3) criteria for good epidemiological practices(GEPs);

(4) principles and applications of good laboratory practices(GLPs).

2. Objective:

In human's ever-continuing search for broader and deeper comprehension of risks, diagnosis, treatment, and prevention of human health disorders, epidemiology has been and continues to be an important scientific tool for understanding etiology and pathogenesis of diseases. Indeed, risk factors traditionally are identified by means of observational, epidemiological studies. Such an approach, however, may suffer from a number of deficiencies. For example, epidemiologic studies generally lack rigorous scientific controls characterizing experiments performed in the laboratory, and

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consequently may not definitively distinguish between the impact of one particular risk factor and the confounding effects of other risk factors. This is particularly true with respect to epidemiological studies focusing on low dose exposures to complex mixtures, in which methods for assessing personal exposure to complex, constantly changing environmental agents are woefully lacking. Moreover, despite the long history epidemiological methods and approaches have enjoyed, there is a lack of standardization in their practice and application, which in turn hampers further progress in the advancement of this scientific discipline.

In recent years, there is a growing awareness among epidemiologists of urgency to tackle methodological issues on measurement of personal exposure to complex, environmental agents. Equally important is need to develop a set of general guidelines and principles (herein referred to as good epidemiologic and laboratory practices, GEPs and GLPs), which, when applied properly and consistently, would be expected to reduce concerns of study qualities and allow data obtained in different locales, regions, and environments to be compared more directly and equitably.

The proposed workshop is intended to introduce and discuss better methods of assessing environmental exposures, as well as principles, concepts and applications of GEP and GLP, for the purpose of bringing epidemiology to a higher level of scientific rigor and uniformity which, in turn, would make it a more powerful tool in studies of etiology and pathogenesis of human diseases.

3. Themes:

- Discuss methods used to measure a person's exposure to a dynamic, complex mixture of pollutants.
- Introduce basic concepts and applications of GEP.
- Presentation and discussion of specific examples where lack of GEP leads to premature or erroneous conclusions.

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- Discuss methods for determining relevant and important biomarkers in the context of exposure to environmental chemicals. Lay foundations for good laboratory practices.
- Discuss meta-analysis, p-trend analysis in relation to good epidemiologic practices.
- Discuss a preliminary proposal which to be carry on five cities of China.

4. Organizers and Sponsors

Center for Indoor Air Research, U.S.A.
Guangzhou Medical College, China
New York Medical College, U.S.A.
Chinese Epidemiological Association

5. Scientific Advisory Committee

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6. Local Committee

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7. Dissemination of information presented at the workshop:

- Spiral-bound notebook containing text of presentations at the meeting in English & in Chinese.
- Meeting report to be sent to the following scientific journals and publisher :
  - Chinese Journal of Epidemiology (in Chinese)
  - Indoor Air Research Series (in English)

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10. Participants

- Invited scientists from outside of China (8)
- Invited Chinese scientists (16)
- Workshop registrants (50)
- Workshop staff (6)

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11. General Timetable

July 14 *Monday*	*July 15* *Tuesday*	*July 16* *Wednesday*	*July 17* *Thursday*
8:00 - 18:00 Registration	8:00 - 9:00 Special lecture	8:00 - 9:00 Special lecture	8:30 - 17:00 Tour Sightseeing in Guangzhou city Lung cancer study in China meeting of the planning group
	9:00 - 10:00 Session 1 lecture	9:00 - 10:00 Session 3 lecture	
	10:00 -10:30 Break	10:00 - 10:30 Break	
	10:30 - 12:00	10:30 - 12:00	
	12:00 - 14:00 Lunch	12:00 - 14:00 Lunch	
	14:00 - 15:00 Special lecture	14:00 - 16:30 Lung cancer study in China	
	15:00 - 16:00 Session 2 lecture		
	16:00 - 16:30 Break		
	16:30 - 17:30	16:30 - 17:30 Closing session	
18:00 - 19:00 **Opening session** Opening remark: Dr. Du Ying-xiu Welcome speech: Dr. Zhong Nan-shan CIAR introduction: Dr. Max Eisenberg			
19:00 - 21:00 Reception		19:00 - 21:00 Banquet	

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12. Program

15, July, (Tuesday), 1997

Session A chairs :	**Dr. G. Matanoski,** Dr. Yu Shun-zhang
8:00 a.m.-9:00 a.m.	
Special lecture	
Dr. John D. Graham :	The rise of epidemiology in risk assessment
9:00 a.m.— 10:00 a.m.	
Session 1 lectures :	*Epidemiologic Methods I*
Dr. Wei Cheng-yu :	Epidemiology and public health policy in P.R of China
Dr. Linda Koo :	Unresolved issues from epidemiologic studies on lung cancer risk factors among Chinese women
Dr. Geng Guang-yi :	Some problems of low risk assessment and promoting quality of epidemiological practices
10:00 a.m.— 10:30 a.m.	Coffee Break
10:30 a.m.— 12:00 a.m.	
Session 1 lectures :	*Epidemiologic Methods II*
Dr. Xu Zhao-yi :	Goals and methodology to explore the cause of lung cancer in females based on time trend analysis of disease development
Dr. Wang Sheng-yong:	Etiologic fraction analysis for case-control studies
Dr. Gao Yu-tang :	A case-control study among female lung cancer
Dr. Wang Qing-sheng:	Using cancer registry as an approach for assessing cancer risks associated with occupation and industry
12:00 a.m.— 14:00 p.m.	Lunch
Session B chairs:	**Dr. Linda Koo,** Dr. Xu Zhao-yi
14:00 a.m.— 15:00 p.m.	
Special lecture	
Dr. S. Tominaga :	Risk factors of lung cancer from a cohort study in Nagoya, Japan
15:00 p.m.— 16:00 p.m.	
Session 2 lecture :	*Diet and Cancer*
Dr. Ragnar Rylander :	Biological factors as confounders for chemical agents
Dr. Guo Cun-san :	Variation of diet habits and human health in China
Dr. Yu Shun-zhang :	Drinking water and primary liver cancer in China
16:00 p.m.— 16:30 p.m.	Coffee Break
16:30 p.m.— 17:30 p.m.	
Session 2 lecture :	*Application of molecular biology in epidemiologic studies*
Dr. Guo Cun-san :	A brief introduction to molecular epidemiology in China
Dr. Zhang Qiao :	Biological markers in environmental health research
Dr. He Ling :	Diet and antioxidants-a nutritional intervention study

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16, July, (Wednesday), 1997

Session C chairs :	**Dr. John D. Graham, Dr. Wei Cheng-yu**
8:00 a.m.— 9:00 a.m.	
Special lecture	
Dr. G. Matanoski :	Epidemiologic study in situations with low-risk
9:00 a.m.— 10:00 a.m.	
Session 3 lecture:	*Environmental agents and cancer*
Dr. K. Phillips FRSC:	Monitoring personal exposures to environmental pollutants
Dr. Wu Zheng-lai :	Analysis of relationship between tobacco dust exposure, smoking behavior and death causes in tobacco factories
10:00 a.m.— 10:30 a.m.	Coffee Break
10:30 a.m.— 12:00 a.m.	
Session 3 lecture :	*Environmental agents and cancer*
Dr. He Xing-zhou :	Lung cancer risk from PAH emissions in indoor air
Dr. Joseph M. Wu :	Markers of environmental chemical exposure and studies of protective dietary factors in epidemiological investigation
Dr. Du. Ying-xiu :	Good epidemiological practices and research on etiology of lung cancer
12: 00 a.m.— 14:00 p.m.	Lunch
Session C chairs :	**Dr. Du Ying-xiu, Dr. Ragnar Rylander**
14:00 p.m.— 16:30 p.m.	**Discussion on lung cancer study in China**
16:30 p.m.— 17:30 p.m.	
Closing session	
Dr. Joseph M. Wu :	
Dr. Max Eisenberg :	
19:00 p.m.— 21:00 p.m.	
Banquet	

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International Workshop on Risk Assessment and Good Epidemiological Practices

Chinese Epidemiological Association

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July 14-17, 1997
Guangzhou, People's Republic of China

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The Rise of Epidemiology in Risk Assessment

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Introduction

In the United States, the regulation of human exposures to health, safety, and environmental hazards is informed by an analytic process called risk assessment. Risk is the chance of an adverse outcome. Defined narrowly, "risk assessment" includes the identification of hazardous exposures based on science, the quantification of risk based on exposure and dose-response information, and the characterization of risks according to how much is known ("uncertainty") and how much the risk varies among subgroups of the population of interest ("variability"). When scientific data are deficient, a risk assessment may still be performed based on plausible assumptions or models that cannot yet be verified (Thompson and Graham, 1996). U.S. regulatory agencies and commercial enterprises now use the results of risk assessments to help inform decisions about how much protection will be provided when hazards are identified in the workplace, in consumer products, and in the environment.

The phrases "risk assessment" or "risk analysis" are sometimes used to refer to an even broader set of formal (and informal) analyses including comparative risk assessment, risk-tradeoff analysis, risk communication, cost-benefit analysis, cost-effectiveness analysis, decision analysis, and lifecycle analysis. For example, the Society for Risk Analysis is an international organization of 2,400 scientists and engineers who are interested in the development and application of all of these risk-related tools. The SRA's journal, Risk Analysis, routinely publishes a variety of peer-reviewed articles on a wide range of risk-related tools and issues. In this article, I have in mind the broader definition of risk analysis but most of what I have to say is relevant to the narrower definition as well.

In recent years, epidemiological information has played an increasingly critical role in risk assessment and regulation in the United States. I define epidemiological information to include all nonexperimental, observational data involving human exposures and health outcomes in a study population of significant size. The increasing influence of epidemiology in risk-related decisions has occurred in the United States, despite the fact that there are no rigorous guidelines in place regarding how epidemiological information should be interpreted and used by risk regulators (Graham, 1995).

In this article, I examine why epidemiology is becoming more prominent and influential in risk regulation, what some of the current applications (and controversies) are in the United States, and what steps might be taken to enhance the quality of the communications and collaborations between epidemiologists, risk assessors, and regulators. I shall leave it the reader to make his or her own judgments about which aspects of the U.S. experience are relevant to China.

The emergence of epidemiology

When deciding whether an exposure of interest is hazardous and whether the

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corresponding risk warrants protective action, the historical tradition in the United States has been to rely on experimental data regarding the experience of rodents or, to a lesser extent, human volunteers in controlled settings. Most new products (e.g., prescription drugs, pesticides, and chemicals) must, as a condition of pre-market approval, be subjected to substantial experimental testing that support their safety under normal or expected conditions of use (Graham, 1995). The randomized controlled clinical trial (RCCT) is often considered the gold standard of safety studies and remains the centerpiece of empirical science in many biomedical settings. Even for exposures to a ubiquitous pollutant such as carbon monoxide (CO), the prevailing health-based standards in the United States are based primarily on experimental studies where angina patients report the time to onset of chest pain at differing levels of CO in the air (Graham and Holtgrave, 1991; Graham, 1991).

As important as controlled experiments are, there has also been an explosion in the role of epidemiology in public health regulation since World War II. A variety of forces have contributed to the increasing interest in epidemiological approaches to risk assessment and regulation.

Errors in estimating human risk based on nonhuman data

Concerns have been raised that safety determinations based entirely on experimental studies of nonhuman subjects may lead to invalid inferences about human risk. (Clinical trials with human volunteers are a possible solution but face increasing ethical constraints due to intensive reviews by committees charged with protecting the rights of human subjects). Concerns about both false-positive and false-negative errors have been raised when human risk is inferred from nonhuman data.

In the case of human consumption of saccharin, for example, early rodent tests indicated a causal relationship between high doses of saccharin and the incidence of bladder cancer. An effort to ban this artificial sweetener was blocked in the USA when the public and elected officials protested the loss of this popular consumer product. It is now apparent based on findings from both large-scale epidemiology of saccharin users and mechanistic toxicology, that saccharin does not pose the cancer risk to humans that was initially expected based on chronic toxicity tests of rodents (Cohen and Ellwein, 1990). In the history of U.S. risk regulation, the attempted ban of saccharin is now considered a clear case of false-positive error based on overinterpretation of crude toxicology data.

In the case of cigarette smoking, the carcinogenic effects of mainstream smoke were not widely accepted in the early 1960s, even after extensive animal testing. It took persuasive positive results from numerous epidemiological studies to cause widespread recognition of the powerful effects of smoking on the development of lung cancer as well as a variety of other disease endpoints (U.S. Public Health Service, 1964). Here a complete reliance on toxicology might have caused decision-makers to commit a huge, false-negative error.

It is now well recognized in the United States that it is not wise to rely exclusively on experiments with nonhuman subjects when performing risk assessments of products/substances that are associated with widespread and sustained exposures in human populations. Suspicions that experimental data may be inducing false inferences about human risk are now stimulating large-scale epidemiological investigations in numerous settings.

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Out of concern about possible false-negative error, epidemiological studies are now underway regarding human exposures to diverse technologies ranging from chemical pesticides to automobile airbags. Toxicological data suggest that farmers can apply pesticides, insecticides, and herbicides on the farm with little or no risk of acute or chronic adverse effects (assuming that such products are used according to safety instructions). Nonetheless, the U.S. National Cancer Institute has launched an ambitious, prospective study of 75,000 farmers in two states (Iowa and North Carolina) to determine whether farmers (or their spouses and children) are at elevated risk of adverse health effects from use of these chemical products (Alavanja et al., 1996). In the case of airbags, experimental testing with dummies and cadavers led to the inflation parameters now governing the design of airbag systems in 60 million U.S. vehicles. Yet ongoing epidemiological studies of trauma in crashes have suggested that the design of airbag systems are not optimized for the safety needs of the motoring public. The extent of injury-mitigation effectiveness for adults has proven to be less than anticipated while disturbing side effects have been observed among children, short adults, and belted occupants (Ferguson et al., 1996; NHTSA, 1996). No one is questioning whether the concept of airbags is a good idea but serious questions have been raised about whether the current design of these systems should be modified based on the experience documented in epidemiological studies.

Out of concern about false-positive error, epidemiological studies of a variety of known animal carcinogens such as formaldehyde, perchloroethylene, and methylene chloride are being undertaken. In occupational settings, the question has arisen as to whether the risks to workers predicted by rodent tests are observable among workers heavily exposed to these chemicals. In these cases the concerns about false-positive error relate not so much to the qualitative determination of human risk but to the magnitude of the human risk associated with specified levels of exposure. It is often difficult to design epidemiology studies that can validate rodent-based risk estimates (due to limits on the number of workers exposed and their exposure levels), but there is increasing interest in the USA in using epidemiological results to test the accuracy of predictions based on rodent testing (Sielken, 1995; Hertz-Picciotto et al, 1988; Hearne et al., 1987).

Errors in inferences based on human case reports without analytic epidemiology

The clinical case report has proven to be enormously valuable in identifying hazardous exposures and motivating precautionary, preventive actions. For example, the early case reports of aplastic anemia and leukemia among workers exposed to benzene played a powerful role in motivating occupational health measures. In Turkey, for example, the replacement of benzene with toluene resulted in a virtual disappearance of aplastic anemia and leukemia among workers (Graham, Green, and Roberts, 1988).

The case report, however, is not always easy to interpret and the inferences about human risk that are drawn from case reports may not be confirmed in large-scale, analytic epidemiological studies. In the United States, for example, inferences about auto-immune disorders from case reports played a major role in the Food and Drug Administration's restrictions on use of silicone breast implants for breast augmentation. There is now a multi-billion dollar lawsuit in the settlement stages that is based on risk claims rooted in case-report information. More recently, there have been analytic epidemiological studies published that

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examine the health status of large samples of women with and without implants. These studies have called into serious question whether the health effects experienced by many women with implants are causally related to the implants (Berkel et al., 1992; O'Fallon et al., 1994).

Even when a technology is a potent cause of health damage to people, it may not be feasible for the practicing physician to understand what is happening. In the case of smoking and lung cancer, physicians in the 1950s were not easily persuaded that lung cancer was caused by smoking. The practicing physician treated many smokers who did not develop lung cancer and the same physician may have seen cases of lung cancer where the patient had never smoked a cigarette in his or her life. Only through observation of large samples of smokers and nonsmokers in analytic studies was it possible to see clearly that smoking is a major cause of lung cancer.

The limitations of the clinical case report have further fueled interest in analytic epidemiology studies. Each day new theories of technological harm are proposed based on the experiences of particular patients. In the United States, for example, some patients with brain cancer have postulated that their tumors may be attributable to their extensive use of hand-held cellular telephones. The profound public health and commercial implications of this hypothesis have induced the telecommunications industry to launch large-scale epidemiological investigations of customers who use cellular phones to various degrees (Carlo et al., 1997). In the next ten years, scientific papers will be published about whether a variety of adverse health outcomes (including brain cancer) are associated with whether a cellular phone was ever used and, if so, the frequency and conditions of use. A parallel research program in toxicology is underway to test the biological plausibility of various hypotheses.

Case studies in regulatory decision making where epidemiology is critical

There are dozens of important regulatory decisions in the United States that pivot on the proper interpretation and use of epidemiology data. In this section, I offer brief case studies of three such controversies -- particles in outdoor air, electric and magnetic fields from powerlines, and pesticide exposure among farmers -- that illustrate some of the major controversies in the use of epidemiological data in decision making. In each case, scientists and decision makers have made case-by-case determinations without any formal guidelines regarding how epidemiological data should be used in risk assessments and regulatory decisions. In contrast, the federal government has for years followed -- with varying degrees of diligence -- published guidelines on the proper use of toxicological data in regulatory risk assessment (Graham, 1995).

(1) Particles in outdoor air

In the last ten years, the environmental epidemiology community has published numerous articles on the statistical association between the concentrations of particles in outdoor air and a variety of health outcomes, including total mortality, cause-specific mortality, hospital admissions, and other endpoints (Dockery, et al., 1993 and 1995). Many of these studies address acute health effects (i.e., daily variations in mortality counts are associated with daily variations in particle levels, controlling for humidity and/or temperature) while others address the chronic health effects of lifelong exposure to particles in air. Much of this research has been published by my faculty colleagues at the Harvard School of Public Health.

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Based primarily on this body of evidence, the U.S. Environmental Protection Agency has proposed to revamp the health-based standards for outdoor particle concentrations and create a new standard for so-called "fine particles" that are less than 2.5 microns in diameter. Small particles may be more dangerous than large particles since they can penetrate deeper into the respiratory tract and may be more difficult for the body's natural defense mechanisms to handle.

If EPA's proposal is adopted, it may have profound implications for economic development decisions in the United States. Many communities in the USA that are now considered to have "healthy" air by the US government could be placed in "nonattainment" status for particulate air pollution. Nonattainment status means that more resources will have to be invested in emission control programs and, until the new standard is achieved, legal barriers will be placed in the way of a community that seeks to attract new industrial facilities that may provide jobs (yet also contribute to the community's current level of particulate pollution). It is therefore not surprising that many Mayors and Governors fear that EPA's new particulate standard could have strong competitive implications with respect to which states and communities will be successful in attracting new industry in the years ahead.

Without taking a stand on the technical merits of this complex issue, it is already apparent that at least one generic issue has been raised that has broad implications for the future use of epidemiological data in regulatory decision making. The issue concerns the appropriate extent of public access to original data used in published research findings that are then used as a primary rationale for significant regulatory decisions.

In the current US debate about fine particles, no consensus exists about whether the original data from key epidemiological studies authored by scientists from Harvard and elsewhere should be made widely available for intensive scrutiny and reanalysis by analysts from affected stakeholder groups. The original investigators have opposed unlimited public access on a variety of grounds, such as the need to protect the confidentiality of individual-level data and the need to protect the investigators from the hassle associated with responding to poorly done reanalyses of the original data on particles. Instead of offering widespread public access, the original investigators have proposed intensive peer review by a neutral third party called the Health Effects Institute (HEI). This is a reputable research organization funded equally by U.S. EPA and the car industry. An opposing view is that any analyst, whether or not affiliated with HEI, should have access to all original data (for purposes of quality checking and reanalysis) that the government intends to use to support a new regulatory position. It is too early to judge how this controversy will be resolved but there is every reason to expect this type of controversy, regarding public access to original data, to be revisited in future decision contexts unless shared principles are developed.

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(2) Electric and magnetic fields from powerlines

Epidemiological studies have raised concerns that human exposure to electric and magnetic fields (EMFs) from powerlines (and other sources) may be causally related to the development of brain cancer, leukemia, breast cancer, and a variety of other health outcomes. A recent report by the National Research Council of the National Academy of Sciences reviewed much of this evidence and concluded that, although a statistical association between residential EMF exposure and childhood cancer has been found in several studies, a cause-effect

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relationship has not been established. The NRC panel placed considerable weight on the lack of a plausible biological mechanism that might govern the link between EMF exposure in the home and childhood cancer (National Research Council, 1997).

Thus, the EMF controversy raises a fundamental issue about the proper use of epidemiological findings in risk assessment and regulatory decision making. What precisely is the appropriate role of "biological plausibility" in risk assessment when a statistical association between an exposure (or exposure surrogate) and disease has been established in multiple epidemiological studies? Answering this question is particularly difficult because a hypothesis that is judged to be biologically plausible by some qualified scientists may be regarded as far-fetched or dubious by other qualified scientists (Graham, Green, and Roberts, 1988). In the case of the EMF-cancer hypothesis, the most developed biological reasoning concerns a (melatonin-related) mechanism that might explain the development or promotion of breast cancer following EMF exposure. Yet the epidemiological data on EMF exposure and breast cancer are less extensive than the epidemiological data on other tumor types.

It is also not clear which segments of the scientific community should have the greatest influence on questions regarding what is biologically plausible. Some would argue that the opinions of toxicologists should have the greatest weight since they have generated the knowledge base on the biological mechanisms known to govern a variety of toxic processes in the body. Others would argue that epidemiologists themselves should have a role in the deliberations about what is biologically plausible. Some epidemiologists have relevant clinical backgrounds and many epidemiological investigators devote considerable time to studying the available biological literature and developing hypotheses that are worthy of study. The physics community is quite confident that EMF exposures from powerlines and appliances are not causing chronic disease, although some skeptics have asked why the physics community should have a potent role in resolution of this kind of question.

Nor is it entirely clear what it means to say that biological plausibility is established "sufficiently" to permit a risk assessor to move forward, make predictions, and guide regulatory actions. Even for many well-known carcinogens, such as mainstream tobacco smoke, the precise biological mechanisms that govern the development of cancer are not fully understood. In the case of dioxin and human cancer, much is made of the plausibility of "hormonal mechanisms" of cancer causation, but it is not clear how such information is helpful for risk assessors and regulators.

It is well accepted in biomedical science that considerations of biological plausibility have an important role to play in judging whether a cause-effect relationship has been established between an agent and a particular health effect. Yet this consensus does not have an obvious application to the world of risk assessment and public-health regulation, where the burdens of proof are lower (due to the need to take precautionary actions when risks might be large and/or the costs of action small) and the key decisions hinge less on whether a cause-effect relationship exists but on what dose-response functions outside the range of direct epidemiological observation are the most biologically plausible. On these more difficult questions, no consensus currently exists among U.S. regulatory bodies.

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(3) Farmer exposure to pesticides and health outcomes

In order for a pesticide product to be registered in the United States, the recommended conditions of use must be demonstrated to provide safety to the farmers that must apply the products at the appropriate points in the growing season. The safety recommendations now made to farmers often restrict the amount of the chemical applied during each application, the frequency of application, the method of application, and the appropriate clothing and protective gear to wear during application. In many cases these recommendations are supported by a substantial amount of data and experience from toxicology and industrial hygiene. However, it is still possible that farmers (and/or their spouses and children) are at increased risk of disease from exposure to various pesticide products. Consequently, the US government has invested in a large, prospective study of 75,000 farmers in Iowa and North Carolina that is intended identify pesticide-related risk factors as well as other determinants of farmer health and safety.

Although the initial results of this study have not yet been published, it is already apparent that the investigators face a generic challenge in data analysis and interpretation that needs to be understood by risk assessors and regulators. The study is examining the use of several dozen chemicals (active and inert ingredients), a variety of tumor types, and numerous non-cancer endpoints ranging from alteration of menstrual function and spontaneous abortion to various immunological disorders. With numerous chemicals and health outcomes under investigation, it can be anticipated that the investigators will undertake numerous analyses of chemical-disease combinations in search of a positive association. Yet the more "searching" that is done, the more likely it is that a positive association will be found (even if there is no underlying causal relationship between chemicals and disease). This "multiple comparisons" problem is not unique to this investigation but has no simple solution.

One approach is to define and publish primary hypotheses in advance of data collection and analysis. These hypotheses might be based on findings from prior epidemiological studies and/or biological data or theories. The more precise these hypotheses are (and hence falsifiable), the more rigor is brought to the process of data analysis and interpretation. In a sense, the process of analysis becomes a process of hypothesis testing where classical tests of statistical significance have some technical appeal.

Some analysts might argue that it is not important for primary hypotheses to be defined in advance of data collection and analysis. The argument is that what counts is whether biological plausibility could have been established prior to data collection and analysis, based on available knowledge in the relevant fields. If such hypotheses are judged to be plausible by qualified scientists, then it does not matter whether the investigators choose to state them prior to or after data collection and analysis.

There is also scientific value in exploratory analyses of epidemiological data that are intended to be useful in hypothesis generation rather than hypothesis testing. When such findings are reported, however, it is not clear whether statements regarding the statistical significance of particular associations should be taken seriously (even though it may be very tempting for authors or readers to do so).

In summary, statistical associations found in epidemiological data may or may not be supported by a priori hypotheses or even plausible hypotheses (judged ex post). There is no strong consensus in the fields of epidemiology and risk assessment regarding how such

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associations should be interpreted. There is widespread recognition that mischief can be caused by claiming "definitive results" based on associations that were identified only after extensive searching and without the discipline created by a well-grounded, falsifiable hypothesis. Since risk assessors may wish to make use of associations in epidemiological data that were of less interest or of no interest to epidemiologists, there is a need to consider whether epidemiologists and risk assessors need to work together on the appropriate use of epidemiological data in risk assessment.

Steps toward improving epidemiological studies and their use in risk assessment

In 1995 and again in 1996, I collaborated with teams of epidemiologists and other scientists on the general problem of how to use epidemiology in the process of risk assessment and regulation. For me the two meetings (one in Washington, D.C. and the other in London) were both encouraging and somewhat depressing. They were encouraging because it is apparent that there is widespread concern in the field of epidemiology that this young discipline needs to police itself better with respect to quality control in order to make sure that inappropriate inferences are not drawn from studies that are preliminary in nature or simply of poor quality. At the same time, the discussions were somewhat depressing because it became apparent that risk assessors do not understand the science of epidemiology (particularly it's craft-like aspects) yet epidemiologists themselves do not share any broad and well-considered consensus about what should be done to enhance and advance the role of epidemiology in risk assessment. Nevertheless, there were some important recommendations that emerged from the London meeting that I think deserve serious consideration in the future (Federal Focus, 1996). I shall summarize these recommendations and offer some personal comments that may or may not reflect the viewpoints of all of those scientists who developed the recommendations.

Recommendation 1

A commitment to collaboration should be made by epidemiologists and risk assessors that includes (a) sharing of raw data where feasible, (b) exchange of protocols and survey instruments, (c) inclusion of epidemiologists in dose-response modeling exercises, and (d) care and fairness by risk assessors in the critique of original epidemiological studies.

In my opinion, adherence to this recommendation would brighten the future prospects for meaningful collaboration between epidemiologists, risk assessors, and regulators. If this recommendation is not accepted, there is a danger that the process (at least in the United States) will become even more adversarial than it already is, which means a further degradation of public respect for epidemiology, risk assessment, and regulation. Nothing is more damaging to epidemiology and risk assessment than the notion that you can get any answer from these tools that you want, depending upon what the client or decision maker wants to hear.

Recommendation 2

Future epidemiologic studies should be funded and designed with the needs of regulatory risk assessors in mind, including (a) more detailed exposure information (e.g., age-specific

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exposure histories and measures of key confounders), and (b) ample resources for careful dose-response analyses.

My limited experience with epidemiologists and risk assessors suggests that they have somewhat different (yet overlapping) interests. Epidemiologists, like most scientists, are deeply interested in proving that cause-effect relationships do or do not exist. The difference between knowing for sure (100% confidence) that breathing fine particles causes heart attacks and knowing only with 70% subjective confidence that this statement is true makes a big difference to an epidemiologist. He or she may design another huge study (or even an entire career) to increasing the subjective level of confidence in a hypothesis concerning cause and effect.

Risk assessors are less interested in causation and are more interested in computing the magnitude of risk at various exposure levels (assuming that causation is true) and for populations of differing susceptibility to the disease in question. In a sense, the risk assessor is more practical than the epidemiologist because he or she knows that most decision makers cannot await definitive resolution of the causation issue prior to making a decision. It is very important for the decision maker to understand what the size of the risk might be for various people, even though this information demand complicates the design of epidemiological studies. It means that more attention is given to documenting precise variations in exposure levels and susceptibilities among study subjects and making sure that the best available statistical tools are applied to the estimation of dose-response relationships. From a scientific perspective, these considerations (while not unimportant) are of less concern to epidemiologists.

Recommendation 3

Epidemiological study teams, and the peer review panels that evaluate them for funding, should include multidisciplinary expertise from the fields of medicine, pathology, toxicology, industrial hygiene, statistics, and risk assessment, as well as epidemiology.

Among epidemiologists, I have noticed that some lament the declining influence of clinical experience and intuition in the field while others lament the lack of biostatistical rigor in studies that continue to be published in the literature. While these positions are often juxtaposed, they are probably both correct to a large degree.

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Recommendation 4

Peer review should be applied to the use of epidemiologic data in risk assessment, including (a) involvement of the original investigator(s) whenever possible, (b) panels that reflect stature and objectivity in appropriate areas of expertise, and (c) opportunity for public comment, such as that used by EPA's Science Advisory Board.

Rather than comment on this recommendation, I would prefer instead to cite a significant body of literature that shows how the principles of peer review have enhanced the scientific quality and credibility of science used in regulatory decision making (Jasanoff, 1990; Graham, 1991).

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Recommendation 5

Reporting of epidemiologic findings should be responsive, if possible, to the needs of risk assessors, including (a) documentation of rationales for decisions about how data were grouped for analysis purposes, (b) clear distinctions between subjects with small versus zero exposure, and (c) reporting of the extent of pretesting in multivariate modeling in order to allow better interpretation of classical statistical tests.

Transparency in risk assessment is becoming a paramount consideration in the U.S. regulatory process. If "outsiders" cannot discern how scientific data were collected, analyzed, and interpreted by regulatory agencies, then the process of developing a public health regulation is not transparent. Some observers might prefer a return to the "old days" when the judgements of prestigious experts were trusted to the point that transparency in reasoning and analysis were not important or at least not essential. The United States is not likely to move in this direction in the foreseeable future and, in fact, there is every indication that the future policies toward risk assessment and regulation in the USA will place an even greater premium on analytical transparency than exists today (Graham, 1996).

Conclusion

There is a curious paradox in the trend toward greater use of epidemiology in risk assessment and regulation in the United States. On the one hand, there is a sense of confidence that the science of epidemiology can serve society with insights that are useful supplements or complements to the insights that would be provided by the experimental sciences and clinical case reports alone. On the other hand, there is also a degree of mistrust in the science of epidemiology that is evident in the demands for transparency and intensive peer review of findings, though this concern may relate not just to the work of epidemiologists but also to the interpretation that risk assessors will offer to decision makers and the ultimate decisions that public health officials will make. The ratio of mistrust to confidence may be somewhat higher in epidemiological studies that report small relative risks, but it should be remembered that the experimental sciences also have serious obstacles to confront when asked by society to resolve small-risk controversies.

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Epidemiology and Public Health Policy in People's Republic of China

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Epidemiology plays an important role in effecting decisions and changes in public health policies. As a country amidst dynamic transition toward full industrialisation and development, China faces numerous health challenges similar to those experienced by other developing countries. Thus, an important objective for Chinese epidemiologists is to raise the awareness of health policy makers on the nature and complexities of various health care issues currently confronting the nation, as well as future ones the country may face. A complementary goal is to suggest scientifically based strategies and preventive measures to mitigate the development of these health issues and to resolve them timely.

In relating epidemiological findings to health care policies, considerations should be given to the following:

1. Applying the results of epidemiological research to effect changes in policy-making processes

China, with its long history, has had a strong and effective central government-guided management system, whose practice essentially involves decisions being originated and made at the top, which then are filtered down to the local governments where implementation occurs. Such a system makes it essential that policy makers understand the major health issues facing the nation, as well as trends and changes in the science and methodologies of epidemiology. As an example, China's national socioeconomic policy has been to advocate predictable population growth through careful family planning and manageable improvement in the overall quality of life of people through market-oriented economic expansions. Whereas the former policy has gained global recognition, the latter is still far removed from reaching its original goal. On the basis of an epidemiologic study performed between 1988-1990, it became clear that quality of life issues for the population at large can actually significantly impact upon future social and economic developments of the nation. Accordingly, a panel of epidemiologists specifically recommended that better intervention measures should be instituted to reduce birth defects and to improve social support and facilities for those with disabilities.

2. Use of epidemiological research findings to evaluate current health service systems and health care policies

With its large and diverse population base, health care needs in China differ significantly depending on geographical locations and ethnic groups. Epidemiology was used to evaluate and provide a more equitable distribution of health care resources to different regions and ethnic groups, in accordance with their specific needs and unique culture infrastructures.

3. Use of epidemiology to better manage future public health challenges

It has long been recognised in China and in other developed countries that a sound health care policy for the 21st century should revolve around the theme of "prevention first always being

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better than cure later". Practice of such an approach requires that concerted efforts be made to educate administrators of various health service agencies, at all levels, to, by and large, abandon the previous health model of "treatment being more important than prevention". Toward that end, epidemiologists have a special role to play, in terms of educating leaders at all levels, to increase their understanding of epidemiological concepts, data analysis and interpretation. Such an objective can be accomplished through organized workshops and special training programs.

4. Providing a scientific basis for planning health services

In order to meet future challenges of better and more cost-effective health service delivery, China's Ministry of Public Health conducted a 3 year survey and research, resulting in the publication of a special report named "Strategic goals of health care by 2000". The publication represented the collective efforts of more than 200 scientists (include epidemiologists, basic research scientists, health policy administrators) from top level medical universities and local public health agencies. The report utilized good epidemiological principles and practices in different phases of its inception, design, planning, and evaluation. It takes into account existing preventive medical care systems and available resources, all of which were analyzed in the context of service needs and policy implementation potentials. A total of fifteen topical goals, listed below, were recommended:

(1) Health care policy;
(2) Resources for preventive health care and health services;
(3) Prevention of infectious disease and promotion of planning immunization;
(4) Prevention of parasitic diseases;
(5) Prevention of non-infectious disease;
(6) Oral health and prevention of dental disease;
(7) Control of environmental hazards and improvement in the safety of drinking water;
(8) Control of occupational hazards;
(9) Balanced diet and nutrition;
(10) Food sanitation and safety;
(11) Health of children and adolescent;
(12) Maternal and child health;
(13) Health care for the elderly;
(14) Reducing the risk of smoking ;
(15) Health education and healthful behaviour.

5. Use of epidemiological surveillance measures to implement and evaluate public health programs and for controlling diseases

In the past 18 years, the disease surveillance network in China has substantially improved. A computerised reporting system that links China's 30 provinces, autonomous regions and municipalities has been established for diseases and made available to all levels of government. Data collected through the disease surveillance network serve as the basis for formulating health policy and devising strategies for preventing diseases. For example, when 6 provinces around the Yang Zhi River were heavily flooded in 1991, the central government of China, out of serious concern about disease-prevention activities in these provinces, mounted a

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major effort to combat infectious disease. Epidemiologists and other experts were dispatched to the flooded area; prevention guide lines were developed and distributed to the affected provinces. Simultaneously, a system for reporting disease activity on a daily basis was established. Data collected from June to October 1991 indicated that infectious diseases had been controlled effectively during the flood.

The reporting system as it exists now covers the entire population (1.1 billion persons) living in all provinces, prefectures and counties that make up mainland China. Thirty-five infectious diseases are reportable under this system. The Ministry of Public Health of China has convened annual meetings to analyse these data on the morbidity and mortality associated with infectious diseases.

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Unresolved Issues from Epidemiologic Studies on Lung Cancer Risk Factors among Chinese Women

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Abstract

A critical review of epidemiological evidence on patterns and risk factors for lung cancer among Chinese women residing within China and in overseas communities indicate disparate findings. Although all studies find low attributable and relative risks from active smoking, incidence/mortality from lung cancer is highly variable within China, with women from most provinces having moderately low mortality rates compared to other countries. The highest mortalities within China are found in the three largest cities, and the possibility of detection bias influencing these rates is discussed. Case-control studies on Chinese women have focused on air pollutants from cooking and heating fuels, or cooking methods and cooking oils. However, many studies with significant findings did not adjust for income, nor address the issue of recall bias and lay conceptions of etiology influencing the results. Moreover, the risk from specific cooking methods and cooking oils varied between studies, and there was little discussion on how such findings coalesced with historical behaviors or variations between high and low incidence areas or populations. Risks from diet showed two patterns: women in Hong Kong, Singapore, and Taiwan had reduced risk from higher fruit/vegetable consumption whereas women in Shanghai or northeast China had increased risk. The lack of consistency between studies on risk factors and a tendency for researchers to ignore patterns from descriptive epidemiology or historical trends of exposure or disease incidence - may encourage criticisms now being directed at "risk factor epidemiology." These unresolved issues encourage the incorporation of methods from molecular biology for future studies on lung cancer in Chinese women.

Key words: lung cancer, Chinese women, air pollutants, diet.

Introduction

A worldwide review of smoking histories among patients with primary lung cancer found that Asian women were the least likely ethnic group to have had a history of smoking (6-57%) compared with ever-smoked percentages of 70-90% for European and American women or 98% for men on a global basis (1). Furthermore, a comparison of age-adjusted lung cancer incidence rates among nonsmoking women living in the Pacific Basin found that Chinese women, whether residing in Shanghai, Hong Kong, or Hawaii had incidence rates of 15.2 to 20.5/100,000, which were two or more times higher than Japanese, Caucasian, or Hawaiian women who had incidence rates of only 7.3 to 7.5/100,000 (2). These descriptive statistics seem to suggest that Chinese women have high incidence rates of lung cancer that are unrelated to a history of smoking tobacco. Whether this is: generalizable to all Chinese women regardless of residence, a recent or historical phenomenon, due to inhaled or ingested factors, or related to respiratory diseases or other experiences will be critically appraised from available published studies. Emphasis will be placed on consistencies or inconsistencies of findings within a study, between studies, or with

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available descriptive statistics. The possible effects of bias and confounding influencing some study findings will also be highlighted.

Patterns from descriptive statistics

Clues about a disease's etiology can be garnered from its distinctive incidence/mortality patterns over time, by age groups, or its variability between racial/ethnic groups and/or geographic location. In fact, the current debate among epidemiologists "That risk factor epidemiology is placing epidemiology at risk" (3) points to the need that more attention needs to be paid by researchers on how their identified risk factors are consistent or inconsistent with descriptive statistics on exposure prevalence or incidence/mortality patterns over time.

1. Do Chinese women everywhere have high incidence rates?

From the latest edition of Cancer Incidence in Five Continents by the International Agency for Research on Cancer (IARC) (4) lung cancer incidence rates for Chinese women are available in 7 population-based cancer registries: 3 cities in China, 2 areas in the USA, and in Hong Kong and Singapore. As shown in Figure 1 below, the world age adjusted incidence rates for these populations vary threefold, with the lowest being 11.2/100,000 for Qidong City, China, and the highest, 33.2/100,000 for Tianjin, China.

Qidong City, a small city of 1.3 million, is just about 60 km. north of Shanghai (population 12 million) and shares a common Jiangsu provincial cultural area with Shanghai. Yet Qidong's female lung cancer incidence rates are moderately low on a worldwide basis when compared with other IARC cancer registries. Qidong City, however, is more notable for its high liver cancer incidence rates of 89.9/100,000 for men and 24.5/100,000 for women (4). There have been extensive studies on liver cancer there since the 1970's, with an annually published journal in Chinese. Qidong Liver Cancer (5), describing their findings. On the other hand, Shanghai has had international collaborative studies on lung and other cancers since the early 1980's (6). As the largest city in China, Shanghai's medical resources to detect and treat lung cancer is also superior to that available in Qidong City. These differences in treatment facilities and medical research focus might partially explain why Qidong's lung cancer incidence is lower than Shanghai's.

Another influential factor might be the channeling of suspected lung cancer patients living in neighboring areas, but being histologically diagnosed [e.g. by bronchoscopy] and treated in the larger cities [e.g. by thoracotomy, chemotherapy, radiotherapy] which have better facilities to do these procedures. Consequently, detection bias may be inflating incidence rates for female lung cancer in China's larger cities, like Shanghai and Tianjun (with population of 8 million and ranking ad China's third largest city (4)). This factor is encouraged by the fact that the clinical symptoms of lung cancer are sometimes indistinguishable from tuberculosis without more sophisticated and invasive diagnostic procedures. However, these biases are less influential for the high incidence rates found in other more affluent metropolitan areas like Hong Kong and Singapore, which have clearer geopolitical boundaries.

Data gathered from the 1973-75 nation-wide survey of cancer mortality in China (7) provide further evidence of lung cancer's variability among Chinese women. Firstly, from the cancer mortality map, it is apparent that the highest declines of lung cancer mortality clustered

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around the major cities in the coastal provinces. Secondly, as shown in Figure 2 below,, the highest world age-adjusted mortality rates were found in the three metropolitan areas of Shanghai, Tianjin,, and a Beijing. Yet, the world age adjusted mortality rates for the provinces adjacent to these municipalities , i.e. Jiangsu for Shanghai, and Hebei for Beijing and Tianjin, were only about half as high at 5.3. and 7.5/ 100,000 respectively. These patterns support the aforementioned artifactual bias theory, although, other possible factors associated with urban living may also be influential.

If the lung cancer statistics among women in Shanghai versus Tianjin in Figure 1 are compared with those in Figure 2, it is interesting to note that in 1973-75,, the mortality rates for the two cities were about the same at 14.3 and 13.8/ 100,000 respectively. However,, about a decade later, the Tianjin women were having incidence rates more than 80% higher than their Shanghainese counterparts. Recognizing that "Less than 10% of lung cancer patients survive 5 years and 80% and dead within a year of diagnosis" (8),, this large change in relative frequencies is also suggestive of artifactual factors underlying these statistics.

Figure 2 also dispels the impression that Chinese women everywhere have high rates of lung cancer. Although lack of diagnosis may play a role in the lowest mortality areas of Guangxi and Gansu provinces, which are rural and had rates of 1.6/ 100,000, the relatively low mortality rates of under 10/ 100,000 for 26 put of the 30 administrative areas listed in Figure 2 show that lung cancer is not a disease characteristically high among Chinese women. It is also notable that the relatively low mortality rates of 2.9/ 100,000 for Guangdong province and 4.1/ 100,000 for Fujian province, show that the original places of origin for most migrants to Hong Kong, Singapore, and overseas communities are not typified by high risk for lung cancer. These contrasts in descriptive statistics need explanations.

2. Are the areas with high incidence a recent phenomenon?

From the last 3 volumes of IARC's registry data (4, 9, 10) trends in incidence from the early 1970's to late 1980's are available for 6 Chinese populations. As shown in Figure 3 below, incidence rates from the earliest to latest periods consistently increased for Chinese women in Tianjin, Hong Kong, and Los Angeles, and generally remained steadily high for those living in Singapore and Shanghai. The patterns from Shanghai are supported by more recent incidence rates of 18.8/ 100,000 for the period 1987-89 (11). By contrast, Hawaiian Chinese women's incidence rates suggested a slight drop. Overall however, 5 out of the 6 populations showed increases over the 15+ year period or maintenance of high rates.

From the descriptive statistics presented in Figures 1 and 2, it is apparent that only some Chinese populations have high incidence rates of lung cancer. In mainland China, the highest incidence rates are found in the largest metropolitan cites of Shanghai and Tianjin, lower rates in smaller cities like Qidong City, and very low mortality rates in more rural areas. These variations also suggest the possibility of other factors like the availability of medical facilities inflating incidence rates in the largest cities. These problems of coverage and completeness of the Shanghai registry have been recognized by the Shanghai authorities and IARC (11). Reasons for Tianjin's high incidence rates and their rapidly increasing trend in contrast to Shanghai [especially if one assumes that Tianjin's incidence rates in the mid-1970's was similar to Shanghai's because of their similar mortality rates at that time] also need explanation.

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For other Chinese communities like Hong Kong, Singapore, Hawaii, or Los Angeles, whose populations are mostly migrants from Guangdong or Fujian province, their consistently higher lung cancer incidence rates relative to their provinces of origin suggest similar risk factors. Given the aforementioned patterns from descriptive statistics, it is likely that the suspected risk factor(s) among the migrant sub-ethnic groups with high risk are newly introduced items or a result of changed exposure to substances that enhance protection or initiate/promote cancer.

Role of inhaled pollutants

As a respiratory cancer, inhalants are normally the first suspects in its etiology. The following discussion will draw on findings from more reliable epidemiologic case-control studies (12), i.e. those that used population rather than hospital controls and took into account possible confounders like smoking, age, and socioeconomic status. Statistical significance will be defined as findings with p-values ≤ 0.05 or 95% confidence intervals (CI) that do not include 1.00.

1. Tobacco smoke

Studies among Caucasians have consistently shown active smoking to be the most important risk factor causing lung cancer in those populations (1). Reviews of such studies show Western smokers to have relative risks (RR) about 10 to 20 times higher than nonsmokers, and the US Surgeon General estimated in 1985 that some 90% of lung cancers among American males and 79% among females was due to cigarette smoking (13). By contrast, studies on Chinese women in various localities have consistently found that most of their lung cancers are not due to exposure from active smoking. Not only is the percentage of Chinese female patients with a history of smoking very low, ranging from 22-56% VERSUS 70-90% for European and North American women (1), but their attributable risk (AR) and RR from smoking are also unusually low. From an analysis combining data from 8 case-control studies conducted in China, the overall AR is 36% and RR is 2.8 (2), for Singapore women their RR is 3.6 (15), and for Chinese women in Hawaii their AR is 11% and RR is 1.8 (2).

With these low risks from active smoking and suggestive evidence that other powerful etiologic agents are operating, it is probably not surprising that passive smoking is unlikely to be a major risk factor for lung cancer among Chinese women. Firstly, Chinese women do not have exceptionally high levels of exposure to environmental tobacco smoke (ETS) when levels of the urinary metabolite of nicotine, cotinine, are measured. In an international IARC study of middle aged women from racially diverse backgrounds living in 13 geographic areas, Shanghainese women had the lowest readings of urinary cotinine adjusted for creatinine (16). In the same study, Hong Kong women's cotinine were moderately high (ranking fourth highest), but this was probably an artifactual finding due to the creatinine adjustment that inflated the cotinine measurements (17).

In this international study, it is notable that Japanese women and Hong Kong Chinese women had urinary creatinine levels that were around 0.7 to 0.8 g/day versus levels that averaged around 2.0 for women from other geographic areas like the USA (16). Although it is known that meat consumption affects urinary continine levels, low meat consumption is unlikely to be an explanatory factor for the Hong Kong Chinese levels because a 1971 study on per capita

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protein consumption found Hong Kong's levels at 107 grams per day to be higher than that for Australia (101g), New Zealand (107 g), or USA (101 g), and 38% of the protein came from animal sources (18). Perhaps the similarly low urinary cotinine levels of the Hong Kong and Japanese women reflect their low body mass index averaging 23 to 24 kg/m2 versus levels of 26 to 27+ kg/m2 for American and Swedish women in a recent comparative study of lifestyle correlates of passive smoking (19). These results demonstrate difficulties international studies may face when trying to disentangle effects from variations in racial and environmental exposures on biochemical measurements from human tissues.

Results from case-control studies in Hong Kong (20), Shanghai (21), and Taiwan (22, 23) asking subjects whether they had a smoking husband or been exposed to ETS from other sources have not consistently found statistically significant RR associating it with lung cancer risk. Perhaps even more notable is the finding of a large collaborative US-China study among women in Shenyang and Harbin (n=965 patients and 959 controls) that found wives with smoking husbands associated with significantly lower risk for lung cancer (RR=0.7, 95% CI=0.6-0.9) (24). Although the authors' explanation for this finding was that it may have been obscured by exposure to other air pollutants, no evidence to substantiate this reasoning was presented. For this rationale to be applicable, they would have needed to show that passive smoking was significantly but indirectly associated with exposure to another air pollutant from their study like cooking fumes or smoky coal.

Another possible explanation for the north-east China finding is the socioeconomic correlates of having a smoking husband during the years the study was done, i.e. 1985-87. At that time, that part of China was just beginning to undergo economic liberalization and development, and cigarettes were considered to be luxury goods so that packs of cigarettes were highly desirable gifts. Those able to smoke manufactured cigarettes (and especially foreign brands) would be economically more well off than nonsmokers. Hence wives with smoking husbands were likely to be wealthier than those with nonsmoking husbands. It is notable that the northeast china study did not adjust for income in their analyses. This finding of a lower risk from having a smoking husband was also hinted at in a case-control study of women in Hong Kong done in the mid-1970's, which estimated a RR of 0.8 (95% CI=0.44-1.30) for women with smoking husbands (25). Although the RR was not significant, the fact that the RR was lower than 1.0 may have been due to the fact that male smokers in Hong Kong at that time were more likely to be office workers or businessman - a relatively affluent group of people. Hence studies of ETS should take into account other lifestyle factors, e.g. diet, income, etc. that may be correlated with having a smoking husband or family relative at the relevant time (19, 26).

2. Ambient air pollution

The possible association of urban ambient air pollution with lung cancer is encouraged by the following concurrent worldwide trends: cities have concentrated sources of industry and vehicles that emit noxious fumes; lung cancer was a rate disease in the nineteenth century but rapidly increased in incidence in the twentieth century; there were large migrations of rural inhabitants to cities at the same time; and dramatic increases in population numbers and density have increased industrial emissions and the numbers and proportions of people living in cities. On the other hand, contrary factors may be raised: heavy smoke emissions from industrial cities

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in Germany and England were existent in the nineteenth century before the epidemic in lung cancer in the following century; there is evidence from several studies in the United States (27-29) that there was an increase in lung cancer in the first half of the twentieth century unrelated to smoking, better detection, tuberculosis, occupation, etc. that may be due to other lifestyle changes associated with people born in rural areas and migrating to cities (1, 29); and women's exposure to air pollution may have improved when moving to cities because cooking and heating fuels in cities are usually cleaner and better ventilated than rural homes in preindustrial societies. These trends occurred later in China than in West, with increasing air pollution and population density as concentric forces more noticeably affecting lifestyles in the latter half of the twentieth century.

However, there are also other factors that argue against ambient air pollution as a major etiologic factor for lung cancer in overseas Chinese communities like Hawaii and Singapore. From the Pacific Basin study of multi-ethnic groups, Chinese females living in Hawaii had nonsmoking related lung cancer incidence rates that were more than twice as high as Japanese or Hawaiians living in Hawaii (2). Similarly, Singaporean studies have shown Chinese females to have higher female lung cancer incidence than Malays or Indians living in the same city, and within their Chinese sub-ethnic groups, women of Cantonese background have about twice the incidence of those of Hokkien or Chiu Chow backgrounds (15, 30). Since all ethnic groups are breathing the same ambient air, and both Hawaii and Singapore are not characterized by heavy industrial air pollutants, there seems to be little evidence to support outdoor air pollution as a major culprit for these populations.

3. Cooking and heating fuels

Humans, even since the days of Peking Man, have been using fire for cooking and heating for thousands of years. The biofuels used were mostly wood and grass, and their resultant fires are typified by smoky fumes from poor oxygenation and dampness in the fuel. Women everywhere were exposed to these pollutants because it is the task of women in most societies to maintain the health. It is only in recent decades that cleaner household fuels like piped gas, liquid petroleum gas, or electricity have become available - and this is limited to cities in the less developed countries. Hence studies on cooking fuel's influence on lung cancer must take into account different historical exposures within a population. For example, it is likely that women living in Guangdong province, the origins of most Hong Kong Chinese, were and are exposed to much higher levels of air pollution from cooking fuels than Hong Kong Chinese women. Yet their 1973-75 mortality rates at 2.9/100,000 are some 7 times lower than that for Hong Kong during the same period (31). In other studies, if cooking fuel is implicated as a risk factor in a population with rising incidence rates over time, evidence should be presented to show that the type of fuel used has similarly changed in previous decades or that housing conditions have resulted in poorer levels of ventilation. Moreover, personal monitoring is needed to substantiate the levels of air pollution women in different environments really face.

Several case-control studies on Chinese women have looked at cooking and heating fuels, especially coal, as a risk factor. Coal was not a common fuel in the warmer subtropical cities of Hong Kong (32) and Taiwan (23, 33) and no increased risk from coal smoke was found in these studies as well as among women in Shanghai (21). Yet, studies on Chinese women living in the

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colder and poorer areas of northeast and southwest China, who used smoky coal for heating and cooking, have found significantly increased risks. From studies of women in Harbin and Shenyang, those who had 'kangs' (a bed heated by coals) had RR of 1.5 (95% CI=1.1-2.0) and those with coal stoves had RR of 1.3 (95% CI=1.0-1.7) (24). Among women living in the poor rural community of Xuan Wei, Yunnan Provice, the RR associated with smoky coal use was estimated to about 2.6 (34). Although the air particles from indoor coal combustion in Xuan Wei has been found to contain polycyclic aromatic hydrocarbons that are carcinogenic (35), other issues may also need addressing. Both studies in China did not adjust for income. With the fumes from coal being an obvious irritant, alternative fuels which are more expensive but less polluting would be the fuel of choice among wealthier families who are the ones with lower risk for lung cancer. Wealthier families might also have more means to buy fruit and vegetables in the winter, which are important sources of antioxidants but scarce and expensive during this season because they need to be transported in from warmer regions. Additionally, Xuan Wei is famous for its smoked ham, so exposure to the smoking process and its consumption of this possible source of ingested and inhaled N-nitroso compounds should have been have researched. And finally, given the lay belief that respiratory diseases are due to inhaled factors, patients with lung cancer would be more motivated to recall past exposures to smoky fumes than healthy controls (36).

4. Cooking methods and oils

The same problem of recall bias among patients versus healthy controls may be exerting an even larger influence on studies associating cooking methods, especially frying or stir frying, with higher lung cancer risk. The 5 studies on cooking methods, and by implication, exposure to cooking fumes, have reported inconsistent results. The first study on cooking methods, conducted in Singapore, did not find any association with cooking methods (14). Two studies in Taiwan reported contradictory results. One found no significant increases in RR (22) and another found RR of approximate 2 from stir-frying and frying, but not deep frying (23). The latter study also reported that women in kitchens equipped with fume extractors decades earlier also had significantly reduced risk for lung cancer. Again, the confounding effects of wealth may be affecting this finding. Women who lived in Taiwanese homes equipped with electrically powered fume extractors in their kitchens decades ago were wealthier than those without such luxury equipment. With kitchen fume extractors becoming a ubiquitous kitchen appliance in Taiwanese homes in recent years, it is not surprising that the latter Taiwanese study found the RR to be reduced with fume extractor use in recent years (23).

A study of Shanghai women's cooking behavior found a RR of 2.6 (95% CI=1.3-5.0) for more frequent stir frying, a RR of 2.2 (95% CI=1.3-3.7) for boiling, but no significant risk from deep frying with a RR of 1.9 (95% CI=0.5-6.8) (21). Yet the study of women in northeast China found a RR of 1.9 (95% CI=1.4-2.7) from deep frying (24). There are additional problems aside from lay beliefs, recall bias, and inconsistent findings between studies in these associations. Firstly, studies which reported significant RR did not specify whether the cooking frequencies were representative of cooking behaviors in the past, which would be of more relevance since the latency period of lung cancer is several decades. Secondly, the cooking methods of frying, deep frying, or stir frying have been prevalent in Chinese cuisine for centuries so reasons need to be

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given on how these methods can explain increasing incidence in recent decades. Thirdly, evidence should be given that usage of these methods differs by high versus low incidence provinces within China, or between sub-ethnic group like the Cantonese versus Chiu Chow. And fourthly, cooking behavior may be confounded by diet as shown by a study among Hong Kong Chinese women (17).

The three studies which investigated cooking oil also had inconsistent results. Shanghainese women who cooked with rapeseed oil had RR of 1.4 (95% CI=1.1-1.8) compared with those who used soybean oil (21). In Hong Kong, women who used oils other than corn oil had RR of 2.7 (95% CI=1.1-6.2) (37), whereas among Taiwanese women there were no associations between cooking oil types and risk (23). The problem of changing patterns of oil use was illustrated in the Taiwanese report, which slowed that lard was predominant in the earlier decades and vegetable oil in later decades in that society. The Hong Kong results were explained as being due to the prevalent belief among housewives at the time of the study, i.e. early 1980's, that corn oil was healthier than other cooking oils. And finally, the Shanghai data did not take into account historical changes in cooking oil use nor the fact that rapeseed oil was a cheaper cooking oil than soybean oil in their analyses (38).

Role of ingestants

Lung cancer risk estimates from various food items in Chinese communities show two patterns: the direction and estimates of risk for Chinese in Singapore, Hong Kong, and Taiwan are similar to those among Western societies, whereas opposite findings are common for inhabitants in mainland China. For example, greater vegetable or fruit consumption is associated with RR between 0.4 and 0.5 in Singapore (15), Taiwan (22, 23), and Hong Kong (37). However, higher consumption of these foods is associated with RR between 1.5 and 2.0 for women in Shanghai (21) and northeast China (24).

In a review of epidemiological studies on diet and lung cancer around the world (39), it was noted that some studies (1) findings may be influenced by inadequate adjustment for behavioral correlates of smoking, or representative of health seekers in a particular society. In Westernized and more affluent societies, smokers tend to eat less fruit and vegetables, whereas health seekers eat more of such foods. However, in mainland China in the mid-1980's, with less influence from the West and a less developed economy, fruit and vegetables were consumed by the poor. The wealthy and health conscious ate meat, which was vastly more expensive (up to 100 times more per kilogram than vegetables) and considered to be more "nutritious". It is therefore not surprising that higher fruit and vegetable consumption is associated with reduced risk in the three more affluent, developed, and Westernized and poorer cities in mainland China. With increasing Westernization and economic development in China, especially in the larger cities, it might be expected that future studies will find the direction and significance of dietary risk factors to be more similar to Western patterns.

Role of previous lung diseases

All studies with results on history of respiratory diseases like chronic bronchitis, pneumonia, tuberculosis, or emphysema reported that one or more of these diseases were significantly associated with increased risk. The RR ranged from 1.4 to 4.7 (21-24, 38).

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However, no single respiratory disease was consistently found to be associated with elevated risk in all the studies which enquired about that symptom. There are also problems of bias that may be uncontrollable because they used the case-control retrospective method: diagnosis bias (that persons with a previous history of tuberculosis or other respiratory disease would be more likely to have a chest x-ray and therefore be diagnosed with lung cancer), recall bias (that lung cancer patients would be more likely to spend the time and energy to recall pasts experiences of lung diseases like pneumonia), lay beliefs (persons with lung cancer would be more likely to think that their previous history of lung diseases had "weakened" their lungs and made them more susceptible to lung cancer), and prodromal symptoms (e.g. the cough and phlegm associated with chronic bronchitis may be linked with early signs of lung cancer).

Future directions for research

This critical review of epidemiologic studies on Chinese women, all of which were of the case-control design, has shown areas where unresolved issues exist. When comparing results from studies on Chinese women in Singapore, Taiwan, Hong Kong, Shanghai, and northeast China, there was a lack of consistency in the identification, direction, and RR estimates for most risk factors. The problems of confounding and bias explaining some of the findings have been highlighted. Many studies also did not relate their findings to patterns from descriptive epidemiology or historical trends of exposure of disease incidence - especially if such data did not support their findings. So where do we go from here?

On the one hand, what is consistent is that Chinese females are unusual in having a low attributable risk from active smoking, and those living in some localities have unusually high incidence rates. These characteristics strongly suggest the need for more research. On the other hand, there may be limitations to the simple questionnaire-style case-control method in identifying causative factors. "Risk factor epidemiology" is coming under increasing criticism from within and without the profession (40, 44). With the rapidly changing lifestyles and exposures in mainland China, cohort studies may also be of limited value, since the latency period of lung cancer is 30 to 50 years, and any cohort study undertaken now would have to constantly monitor future changes. It may also be too late to initiate a cohort study in Hong Kong or Singapore, because more recent incidence data from both areas indicate a leveling off of incidence rates in recent years.

The rapidly expanding field of molecular epidemiology, whereby biochemical markers of exposure, or better yet, molecular fingerprints of biological change and DNA mutations offers promise to overcome the problems of inaccurate assessments of exposure status or bodily changes as a result of such exposures. For example, specific mutations on the tumor suppressor gene, p53, is associated with specific carcinogen exposures such as tobacco smoke, aflatoxin, and ultraviolet radiation (42). A recent study of p53 gene mutations in samples of lung tumors from Chinese women in Hong Kong indicated an unusually high prevalence of single-base deletions (43). Measurements of DNA adducts (44, 45) antioxidant status (46), and DNA damage (47) can be added to future exposure studies. The application of developments in molecular biology may help solve the mystery of why Chinese women in some communities have an unusual propensity to succumb to lung cancer.

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FIGURE 1
Lung Cancer Incidence Rates Among Chinese Female Population

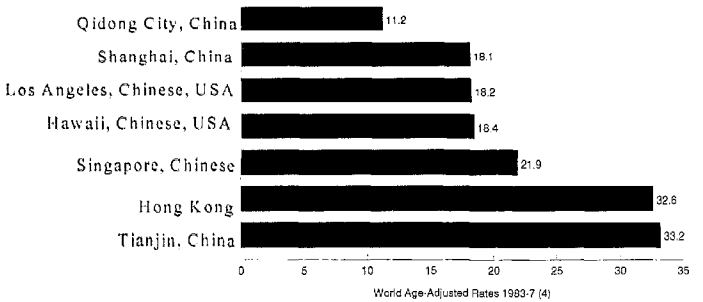

FIGURE2
Female Lung Cancer Mortality in China, 1973-5

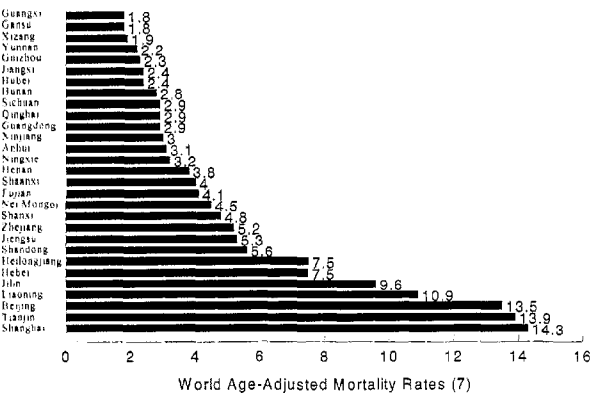

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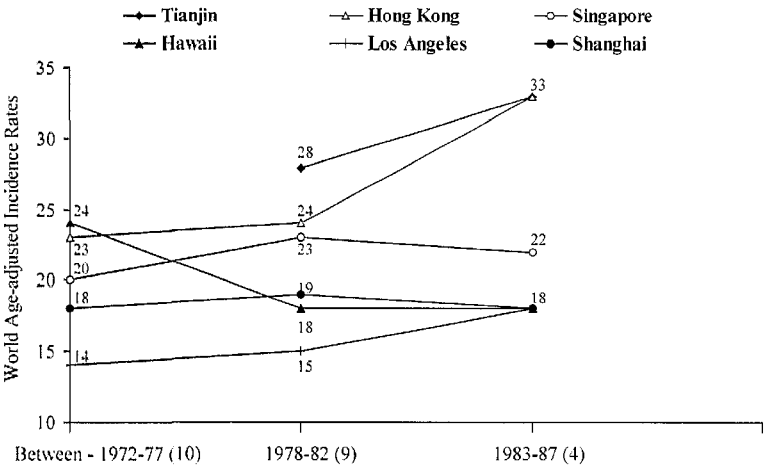
FIGURE 3
Trends in Lung Cancer Incidence Among Chinese Female Populations



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Changing Diets and Their Correlations with Cancer Incidence Trends in Hong Kong

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Introduction

From the early 1960's to mid 1990's, the metropolitan area of Hong Kong, an urban Chinese society under British colonial rule on the southern tip of China, underwent great economic and social change. Monthly household expenditures on all items increased from approximately U.S. $100 in 1963-1964 to $2,424 in 1994-1995 -- an increase of some 2400% over the approximately 30 year period. The corresponding changes in dietary habits and their correlations with site-specific cancer incidence trends over this period will be analyzed in an ecological study.

Methods

Data on cancer incidence from 1973 to 1992 were obtained from the population-based Hong Kong Registry, with chi-square tests for trend calculated to test the statistical significance of site-specific changes over this period. The age specific curves for each cancer site for 3 cohorts of the periods 1973, 1980, and 1990 were also studied.

Data on food purchasing behavior and retail prices for 8 common foods were obtained from the Hong Kong government's household expenditure surveys, which began in 1963 and have been conducted about every 5 years. Their method of random stratified sampling of subject households was designed to be representative of households in Hong Kong, with e.g. 2793 households surveyed in 1963-64, and 5,591 in 1994-95.

Findings

Cancer incidence rates from 1973 to 1992 showed that lung and colon cancers significantly increased, and nasopharyngeal cancer significantly decreased for both sexes. Additionally, cervical cancer and male esophageal cancer significantly declined, whereas changes among the following sites were of borderline significance: decreasing male laryngeal and female esophageal, and increasing prostatitic and female breast cancers.

Calculations from household expenditure data on specific foods/food groups and marker prices for similar foods for the period 1973-74 to 1994-1995, indicate that rice ($p<0.001$) and egg ($p=0.097$) intakes per person have generally declined, but consumption of fresh water fish ($p=0.038$), fresh vegetables ($p=0.006$) and locally slaughtered pork+beef+poultry ($p=0.064$) have increased.

By combining both sets of data, correlation coefficients were calculated for changes in per capita consumption of these foods with cancer incidence data of the same year or lagged 10 years later. Higher meat intakes were significantly and positively correlated with cancers of the

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colon, rectum, prostate, and female breast. The correlations also suggested that current diets were more influential than diets a decade before for cancers of the lung, esophagus, rectum, and prostate. Cancers of the nasopharynx and colon were significantly correlated with both current and past diets.

Conclusion

Although these results should be interpreted cautiously because of the problems of ecological bias and confounding [since the data are based on whole populations and the exposure status of those with or without disease is not known] ecological studies are useful for hypothesis generation and can be used on readily available descriptive data on whole populations. The findings from this study support the hypothesis that increasing intakes of meat and its associated fat are risk factors for increases in colon, rectal, prostatic, and female breast cancers among Hong Kong Chinese.

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Some Problems on Low Risk Assessment and Promoting the Quality of Epidemiological Practice

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1. Strength of association and the significance of RR or OR

Epidemiologists use the term "risk factor" as that which by itself is not sufficient to be a causative factor, but has positive association with the disease being studied (1). Usually the relative risk (RR), or odds ratio (OR) and its 95% CI (confidence interval), and p value are used to evaluate the strength of the association between the risk factor and the disease in question. P values of <0.01, <0.05 or >0.05 are used to express the degree of significance. The p value is considered to be significant when the 95% CI does not include the null value 1.0, i.e., $p<0.05$. Otherwise the p value is considered to be not significant.

Usually the criteria listed in the Richard Manson's Occupational Epidemiology (1980) are used to express the strength of the association between the risk factor and the disease (2,3). The criteria are as follows: RR (OR) 0.9-1.1, no association; 0.7-0.8 or 1.2-1.4, weak association; 0.4-0.6 or 1.5-2.9, medium association; 0.1-0.3 or 3.0-9.9, strong association; and <0.1 or 10, very strong association.

There are different opinions about the significance of RR (OR) values (4). Doll of Oxford considers the RR value to be significant when the lower limit of the 95% CI falls above a threefold increase in risk, whereas Trichopoules of Harvard suggests that RR value is significant only when there is at least a 4-fold increase in risk. Some journals such as the New England Journal of Medicine requires the RR to be above 3 before a finding becomes acceptable for publication, whereas the FDA suggests that if the RR is not at least 3 or 4, the merits of the findings are questionable.

2. Studying risk factors is a main task in epidemiology

Epidemiology was the tool of choice for analyzing the high RR (OR) risk factors, such as the relationship between cigarette smoking and the risk of lung cancer. Since the level of the exposure to the risk factor (cigarette smoking) can be quantitatively calculated, and the clinical outcome of lung cancer is not difficult to diagnose, the association between cigarette smoking and lung cancer has very high RR values. Thus, almost all studies gave similar results. The relationship between cigarette smoking and lung cancer was investigated by Wynder (1950) who reported a value of RR so large that it justified smoking as being causally associated with bronchogenic carcinoma, even without the support of statistical data (5). Other studies, such as the relationship between alcohol drinking and cancer of upper alimentary tract, the association between radiation and leukemia, the influence of sexual behaviour on increasing the risk for cervical cancer, are, for the same reasons, easy to perform, even by less experienced epidemiologists (6).

Recently, external factors (such as diet, lifestyle, environmental factors, etc.) have taken on increasing importance as risk factors for numerous debilitating diseases. The substantial increase in the incidence and mortality rate of cardiovascular disease noted in the last few

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decades, cannot be easily explained on the basis of changes in internal human factors. Although 70%-90% of cancers are considered to be related to human external factors, only a small number of the risk factors has been identified, let alone understood. Thus, there is strong push for epidemiologists to study the subtle links between diet, lifestyle or environmental factors and a variety of diseases in humans. The RR (or OR) of these alleged risk factors is usually <2. Muscat et al. (7) studied the relationship between exposure to environmental tobacco smoke and the risk of heart attack, and reported that although there was a 50% increase in the risk of myocardial infarction (OR=1.5), the elevation was without statistical significance. Gomes et al. (8) studied the risk factors for breast cancer, and reported an OR of only 1.43 (95% CI 0.93-2.21) for cigarette smoking and an OR of 1.16 (0.68-1.97) for alcohol drinking. Gajalakshmi et al. (9) investigated cigarette smoking in relation to stomach cancer, and reported an OR of 1.5-2.4 for age starting to smoke, and a different OR of 1.6-3.1 for amount of cigarettes smoked. However, all of the 95% CI included 1.0. Wu et al. (10) studied the family history of cancer and risk of lung cancer among life-time non-smoking women, and reported that the OR of respiratory tract cancer was 1.3 (95% CI 1.0-1.5), whereas the OR of all forms of lung cancer was 1.52 (1.0-1.22). Correspondingly, the ETS (environmental tobacco smoke) adjusted OR was 1.30 (0.9-1.8) and 1.5 (1.0-2.2).

3. Controversies in weak associations studies

Different laboratories frequently reported conflicting and even contradictory results when studying weak associations. Taubes (4) reviewed many such studies in a publication entitled "Epidimiology Faces Its Limit". Weak associations included studies of the relationship between exposure to residential radon and lung cancer, in which positive associations were reported by a Swedish study, with no associations found to be present between residential radon and the risk of lung cancer in a Canadian study. Conflicting results also abound in investigations on the associations that possibly exist between exposure to pesticide residue, e.g., DDT, and the risk of breast cancer. Studies of the electrical utility workers in the United States suggested a positive link between exposure to EMF and the incidence of brain tumor, whereas a similar study in Norway on the relationship between EMF and frequency of lymphoma and leukemia in 0-14 year olds failed to report any association (11). Taubes (4) also noted that many controversial reports by the public media have appeared concerning the possible link of some alleged risk factors and a variety of diseases. Examples include: influence of hair dyes on lymphoma, myeloma and leukemia; relationship between coffee consumption and pancreatic cancer and heart diseases; use of oral contraceptives and other hormone therapy with many diseases of women. Because of the publicity surrounding these controversial results, and the lack of proper scientific perspective and interpretations for the reported findings, the public often goes through wide swings of emotions, creating an "epidemic of anxiety" (which actually was first described a decade ago by Lewis Thomas) (4). In an editorial that appeared in the New England Journal of Medicine, it was pointed out that the health-conscious Americans "increasingly find themselves beset by contradictory advice. No sooner as they learn the results of one research study than they hear of one with the opposite message." "They asked " What should the Public Believe?"

4. Is there any significance for weak associations?

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Although some epidemiologists consider an association with RR of less than 2-3 to be not significant, others hold the view that even if the risk increases by 10%, it can be significant provided consistent results were reported in many studies. Wynder (6) disagreed with the view that any RR of less than 2 should be disregarded. It was suggested by Wynder that even when a risk factor produces a RR of 1.2 or 1.3, it can have a major public health impact provided it is epidemiologically established as a causative factor (6). For example, if a disease has a high prevalence rate, a low RR may still be important. As an example, a risk factor with RR of 3 for a disease with prevalence rate of $3/10^5$ can be expected to increase by 2 patients in a population of 100000, a different risk factor with a much lower RR of 1.2 for a disease with prevalence rate of 12% ($12000/10^5$), however, may be expected to increase by 2000 patients (which is 1000-fold higher than a risk factor with RR of 3 for a disease with a lower prevalence rate). It should be noted that weak associations often become excluded as confounding factors in statistical analysis, e.g., logistic regression analysis. Thus, greater attention should be given to weak associations, especially when it comes to diseases with high prevalence rate or those with serious clinical outcome.

5. How to increase the strength of the weak associations?

5.1. Is the sample size large enough?

Increase the sample size may narrow the 95% CI and lowers the p value.

5.2. Meta-analysis

Meta-analysis is a technique for combining ambiguous results of many studies in order to conclusively demonstrate whether a similar trend exists for all studies used in the meta-analysis. Meta analysis may not resolve controversies concerning the results or interpretations. Willet studied the relationship between alcohol consumption and breast cancer, and suggested that because more than 30 of the 50 published studies reported alcohol drinking to increase by 50% the risk of breast cancer, an association does exist between alcohol drinking and breast cancer. A different conclusion was reached by others (4).

Thomas performed a meta-analysis on the link between longterm oral contraceptive use and breast cancer and concluded that a modest risk exists between the two. The same analysis conducted by Weiss led to the conclusion that although a small increased risk was associated with oral contraceptive use, the meaning of the association was not clear.

It should be noted that in meta-analysis, it is important to minimize biases by including the data from the studies with different designs, methodologies and subject groups (4).

5.3. To perform trend tests for the low risk factor using quantitative measurements of different levels of exposure to the alleged risk factor. Gajalakshmi, et al. (9) studied the relationship between smoking and stomach cancer, and reported that although 95% CI for every exposure factor includes 1.0, the trend test, nevertheless, showed a $p<0.01$, suggesting that amount of smoke exposure may have an association with stomach cancer. In the case of the relationship between EMF and brain tumor, lymphoma and leukemia, Tynes showed no association even in the trend test analysis, strongly suggesting that no association existed between EMF with the

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diseases in question (11).

5.4. Control biases and confounding factors. It is known that biases and confounding factor exist in the design, survey, analysis and even publication of the results of analysis of risk factors, making the reported results subject to different interpretations (1,12). Smoking may confound any study on the relationship between alcohol drinking and any forms of cancer. Some factors, such as race, age, sex, that should not be considered as confounding, actually ended up being considered as confounding factors. Wynder suggested that "wish bias" (13) may subconsciously lead researchers to consider his/her results as causality and creates a similar impression on the readers. The "wish bias" of the publishers also may make them less likely to publish papers with low associations or with strong associations.

5.5. Improving technologies and methods for objectively measuring the levels of actual exposure to an alleged risk factor. Some exposures and the amount of exposure can be easily estimated (such as: smoking habit, duration and amount of smoking), whereas many other factors (such as radon exposure) can not be easily measured. Some factors (such as cups of coffee drunk per day, or the amount of fat taken per day) may be biased by memory recall. When the investigator learns how to measure exposure correctly and objectively, a weak association may become stronger. As an example, only weak associations were found between lung cancer and all steel-worker. However, when the study on the group most exposed to the carcinogens, i.e., cookoven workers, high RR was found. (4).

6. From association to causations

Generally speaking, although high risk associations are more likely to be causal relations, they, in the absence of additional information, should not be equated with causality. The OR of smoking with lung cancer is so large that one could consider it as a causal factor. In the Surgeon General report of 1964, when the evidence on smoking and lung cancer was reviewed, the criteria used for causation were basically the ones recommended by Hill (15) which included the temporal trend analysis, consistency, dose-response, biologic plausibility, as the most important factors. Subsequently modifications of Hill's criteria were made by others (11, 16-19).

Wynder (6) proposed that ecologic comparison of the distribution of the risk factor and the disease is a useful tool to establish causation (6). Using the prostate cancer as an example, Wynder noted the mortality from prostate cancer is 10 times greater in USA than in Japan and China , and that the rate of prostate cancer increased when Asians migrate to the United States. It was postulated that such a finding strongly lends support to the contribution of lifestyle variables for prostate cancer. Other studies reported an increase risk for prostate cancer when a high fat diet, particularly of saturated fat and meat, was consumed (20-22). In the absence of ecological data, high risk as being equivalent to causation must be considered with care. Ideally leads obtained from ecological and epidemiological studies should be supported by experiments performed in the laboratory. For example, although selenium deficiency has been suggested to be causally related to liver cancer, no negative association existed between the distribution of selenium and liver cancer. Without support from laboratory studies, no conclusive statements can be made regarding selenium and liver cancer.

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7. Promoting the quality of epidemiological practice

Epidemiology is most applicable in studying the causes of infectious diseases and high risk non-infectious diseases. Examples in which epidemiology plays a critical role include: successfully controlling and eliminating epidemics attributable to many infectious diseases in the 19th century, convincingly exploring the causal relationship between cigarette smoking and lung cancer in the 1950s, global eradication of smallpox in 1979, and advancing the understanding and possible eradication of dracunculiasis and poliomyelitis. At the Chinese National Scientific Conference in the 1970s, epidemiology was proclaimed by the Minister of Public Health, Professor Qian, Xinzhong, as one of the 6 leading sciences for furthering advances in all branches of medical sciences.

In as far as applications for epidemiology are concerned, the most frequently encounter controversy surrounds the issues related to low risk factors, especially when reports of risks associated with alleged factors are erroneously represented by public media. Even among scientists, opinions regarding the significance of risk factors giving low ORs differ, and range from "Failure of the academic epidemiology" (23), to diametrically opposed views of "epidemiology, rooted in biology and medicine, could provide the knowledge of preventing neural tube deficiency, cardiovascular diseases, cancer, HIV infection, etc." (24). As pointed out by Wynder, "If epidemiology is conducted properly, it becomes a valuable asset for determining the etiology of a disease and for evaluating intervention. This field of study uniquely can and has contributed significantly to our understanding of the causation of human health and disease" (6). According to Wynder, "epidemiology has and will continue to make new contribution to our understanding of the pathogenesis of disease and their prevention" (25).

Further progress in the application and utilization of epidemiological methods require that the quality of epidemiological practice be improved. The following is a list of recommendations toward that end.

7.1.Epidemiologists must broaden the scope of their science, skills and technological know-how's. Ecological and social-cultural perspectives must be added to the practice of good epidemiology. A good epidemiological study must be properly designed, with biases and confounding factors properly considered, so as to avoid obtaining unreliable results.

7.2.Care must be exercised in making inference on causality based on associations, especially in cases when the RR is low.

7.3. Avoid "wish biases" (6).

7.4. Practice "Quick and Clean" epidemiological study (28), especially in urgent situations.

7.5. Practice the art of objectively and carefully reporting results. Emphasize the need for more investigation, in light of the possibility that "however cautiously the investigator may report his conclusions and stress the need for further evaluation, much of the press will pay little heed to such cautions, by the time the information reaches the public mind, via print or screen, the

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tentative suggestion is likely to be interpreted as a fact." (6).

7.6. Support publication of the negative as well as the positive results, as long as the studies were done with sound scientific methodology. This is especially important since "Investigators who find an effect get support, and investigators who don't find an effect don't get support. When times are enough it becomes extremely difficult for investigators to be objective" (6).

Epidemiology may address the low risk factors, and continue to make greater strides in disease prevention and in health promotion for all people of the world.

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Goals and Methodologies to Investigate the Causes of Lung Cancer in Females Based on Time Trend Analysis of Disease Development

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Introduction

Since the beginning of 1980's, a registration system for the incidence of cancer and all causes of death has been established in the province of Liaoning. Using data from such a registry, previous research from this laboratory has focused mainly on the health effects of atmospheric pollution and occupational exposures in relation to a variety of cancers, such as lung and stomach cancer, respiratory diseases and other diseases. Although some issues concerning the relationship between these risk factors and the diseases mentioned have been addressed and resolved, many others remain to be investigated. This review summarizes our past findings and proposes additional studies for the future.

1. Previous findings and conclusions

A close examination of our published data show the following: although the total death rates for the population in Liaoning have basically remained unchanged over the past ten years, the composition of diseases and the proportionate mortality rate attributable to a specific disease has changed significantly. Adjusted for age, diseases in which the incidence and the mortality rates show significant increases include: lung cancer (3% increase per year), breast cancer, colon cancer, cardio- and cerebro-vascular diseases, endocrine disorders such as diabetes. This trend was similar to what has previously been reported for many developed countries, suggesting that some common factors, probably related to "modernization" in the developed countries, could be involved (Table 1).

2. Risk factors considered to be of primary importance in disease causation

2.1. Smoking should certainly be considered as the most important risk factor, reportedly showing a direct relationship with most of the diseases listed in Table 1, based on reports from numerous published studies. However, its relative risk and attributable risk, insofar as lung cancer is concerned, is considerably lower in Liaoning than those reported in western countries. According to our case-control study with 1250 paired cases and controls, smoking accounted for 2/3 and 1/3, respectively, of the incidence of lung cancer in males and females.

2.2. Both indoor and outdoor air pollution showed positive associations of varying degrees with the risk for lung cancer, cerebral vascular diseases, and COPD. Such a relationship was reported in case-control studies, ecological analyses and time trend investigations. Although the associated risk is low (OR= 1.5), the attributable risk is about 15 % since a relatively large population is exposed to indoor and outdoor air pollutants.

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2.3. Occupational factors. Exposure to PAH and other occupational dusts showed a dose-response relationship (in life accumulated dose) with the incidence of lung cancer. Such a relationship was reported to exist in workers at metallurgy, pharmaceuticals, and ceramics manufacturing industries, where dusty working environments prevail. Except for PAH, which is known to be highly associated with the risk of various carcinomas, the effects associated with exposure to other occupational dusts had an OR of only 1.5. Because only a small proportion of workers were exposed to occupational dusts, the PAR, even for lung cancer in males working in steel industries, was less than 6. The corresponding PAR for female factory workers was even lower.

2.4. People with a family history of disease. A number of diseases listed in Table 1 was positively correlated with a family history of disease, although it is not clear whether this relationship is due to environmental factors and/or heredity influences.

2.5. Protective effects of vegetables and fruits have been established.

In general, less than 50% of the attributable risk in total has been shown to be associated with known risk factors in the case of lung cancer in females.

3. Factors which have yet to be proven to be associated with diseases

Although passive smoking (exposure to ETS) and indoor pollution due to radon have been reported to be risk factors for lung cancer in the western literature, no such associations can be found in our studies. In the case of exposure to indoor radon, essentially the same sampling methodology used in many studies performed in countries outside of China was employed (α-trace sampler placed inside houses for a year). This sampling method gave to accumulated measurements similar to levels reported in US and Swedish studies. However, only very weak association, with no statistical significance, was found in female lung adenocarcinoma. It should be noted that the studies were conducted in 1986 at a time when most of the subjects were also exposed to heavy indoor coal pollution. Whether indoor air pollution from burning coal may act as a confounding factor for the effects of passive smoking or from radon pollution needs to be re-investigated.

4. Puzzling questions with no answers at the present time

4.1. Lung cancer has been rising at the same steady rate in both males and females. However, increases in the prevalence of smoking have largely been restricted to males. Squamus-cell lung cancer is mainly found in males, whereas adeno-cacinoma occurs more frequently in females. Smoking and passive smoking could not explain the increase of lung cancer in females.

4.2. During the past two decades, air pollution and indoor coal pollution have been better controlled, resulting in air quality improvement. About 80% of the homes in Shenyang now use gas for cooking and heating. Such improvements in indoor environments are at odds with the increase of lung cancer.

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4.3. Housing/living conditions, nutritional status, intake of fruits and vegetables have all shown dramatic improvements in the past two decades. Yet, these changes seem to have little influence on the increase of the incidence of lung cancer.

5. Hypotheses

The increase of lung cancer in both men and women requires examination of new risk factors which may be increasing during the past 2-3 decades. Some possibilities are:

5.1.Exposure to ETS. To more definitively study the effects of exposure to ETS, better questionnaire design, coupled with use of more objective markers for assessing exposure, should be used in new studies.

5.2. Since new materials, especially bricks and cement blocks made from smelt slag since the 1960's, are used in construction nowadays, studies are needed to re-evaluate indoor radon content and its effects on the incidence of lung cancer in both males and females.

5.3. Composition of diets and food preferences have undergone marked changes over the past three decades. For example, consumption of oil has increased 10-fold, from 3 Liang (4.2 ounce) to 3 Jin (42 ounces) per person per month in the Liaoning Province. This means there has been a substantial increase of indoor exposure to fried oil smoke and organic volatiles, as well as of fat intake. Their effects on human health and on incidence of lung cancer needs to be further evaluated.

5.4. Change in food composition. More of the calories in the diet come from animal sources nowadays instead of vegetables, as in the past.

5.5. Indoor and outdoor pollution situations. TSP and SO_2 are indicators which had been used in the past. However, according to our study in Shenyang, TSP and PM10 concentrations could be affected greatly by the wind blown dusts, including both natural soil dust and construction dust. Anti-dusting measures, e.g., dust shades in plants and pave streets in cities, could reduce TSP significantly. Moreover, although the coal consumption in the city has been increasing annually, locations of coal burning devices have changed over the years. For example, stoves, instead of being indoors, are now generally placed outdoors. Boiler rooms are more commonly used to provide centralized heating. Given these changes, it is unclear as to whether the most harmful PM2.5 in outdoor coal smoke and the PAH levels have actually increased or decreased over the years. This is an area that needs further study. Also the relationships, if any, between indoor and outdoor pollution, remain to be investigated.

5.6. Genetic factors. The question can be raised as to whether "city risk factors, i.e., urbanization" may actually be confounded by genetic factors. For example, after exposure to occupational or environmental hazards, could the hypothesized mutations that may arise in the genes of the parents be actually transmitted to the offspring, which, in turn, may influence their susceptibility to lung cancer?

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5.7. Other new changes, such as increases in car exhaust emission, decrease of female fertility rate, etc., need to be addressed.

6. Difficulties in past studies and suggestions for solutions

6.1. Recall bias has been a significant confounder. Its effects most frequently relate to collection of food history and past indoor exposure history. Overly long and overly detailed questionnaire may introduce more bias in the data.

6.2. Environmental pollutants usually exist as complex mixtures. The suspended particles vary in their chemical composition. Even in the city, it is hard to measure the exact exposed levels of specific environmental pollutants for each resident. Although the individual difference for PM2.5 may not be very large, more data are required to confirm such an assumption.

In summary, comparison of risk factors for lung cancer between cities requires more precise and objective scientific measurements, and more representative indicators for exposure to the alleged risk factors. Prospective studies, combined with more meaningful biomarker measurements aimed at giving insights on the complexities of the genetic trait (susceptibility), may lead to breakthroughs in our understanding of the etiology and pathogenesis of lung cancer.

TABLE 1
Age-specified incidence (or mortality) rates of major diseases with ascending trend during the recent 10 years (average increase percent per year)

	Male	Female
Lung cancer incidence	3.3	2.2
Lung cancer mortality	3.6	2.5
CVD mortality	7.8	8.7
Stroke mortality	4.2	1.3
Respiratory diseases mortality*	-6.9	-7.5
COPD mortality**	1.2 (ns)	-0.03 (ns)

* not including COPD

** COPD: chronic obstructive pulmonary diseases, not significant for male and female.

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Fractional Analysis of the Involvement of Multiple Risk Factors in the Etiology of Lung Cancer: Risk Factor Interactions in a Case-control Study for Lung Cancer in Females

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Abstract

A 1:1 matched case-control study was conducted in Guangdong province to elucidate the fractional contribution attributed to various risk factors allegedly involved in the etiology of lung cancer (herein referred to as EF) in females. Two hundred female cases with primary lung cancer, identified from 5 hospitals, were matched 1:1 with controls according to age, area of residence, and education. Multiple conditional logistic regression analysis showed that exposure to passive smoke from spouse, poor kitchen ventilation, preference for pickles or salted fish, history of chronic bronchitis, family history of tumour, pulmonary tuberculosis, use of oral contraceptives, were independent risk factors for female lung cancer (OR=2.16~40.55, $p<0.05$). EF of the various independent risk factors were 0.535, 0.432, 0.252, 0.124, 0.115, 0.072, and 0.069, respectively. Interactions between passive smoking from spouse and other risk factors such as use of oral contraceptive, family history of tumour, poor ventilation in the kitchen, history of pulmonary tuberculosis, liking for pickles or salted fish, were also analyzed. The results showed that EP(AxB) (etiologic fraction attributable to interaction) were 0.848, 0.499, 0.479, 0.416, and 0.346, respectively. The interaction indices were 0.906, 0.543, 0.578, 0.427, and 0.441. These findings suggest that passive smoking from spouse, particularly those who had a history of use of oral contraceptives, increases the risk of lung cancer in females.

Key words: etiologic fraction, female lung cancer, passive smoking, interactions

Introduction

Lung cancer has been on the rise every year in China since the 1980s. From 1982 to 1989, the 58 National Disease Detection Centers reported an increase of 14.1% (urban increase 43.7%) in the lung cancer death rate, with an average annual increase of 2% (1,2). lung cancer mortality among females in some area has recently surpassed the breast cancer mortality. Forty percent of female lung cancer deaths in Guangzhou involve nonsomking women, suggesting that risk factors other than smoking may be involved in the etiology of lung cancer. Since involuntary or passive smoking (PS) has been suggested to increase the risk for lung cancer in females, we undertook analysis of various risk factors which allegedly contribute to the etiology of lung cancer, using cases collected from 1992-1995. Interactions between passive smoking and various other risk factors were also analyzed using the Mantel-Haenszel and conditional logistic methods.

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Materials and methods

1. Study subjects

The cases, whose diagnoses of primary lung cancers had been pathologically confirmed, were identified from hospital in-patients in the city of Guangzhou. The controls consisted of patients with non-malignant tumors who were hospitalized at the same hospitals during the same time period as the cases, and who were found to be free of any lung disease. The cases and controls were matched for sex, place of residence, educational level, age (±5 years), and were either Guangzhou natives or residents of Guangzhou for at least 20 years.

2. Survey items

Items included in the survey were general health conditions, history of lung disease, family history of tumors, smoking status, passive smoking (at home and at work), dietary habits, kitchen ventilation, and use of oral contraceptives.

3. Methods of analysis

The data were subjected to single-factor logistic regression analysis, Mantel-Haenszel analysis and conditional multi-variate logistic regression analysis. In addition, the etiologic fraction (EF), and preventable fraction (PF), were analysed using the following model .

EF=P(OR-1)/{P(OR-1)+1}or EF=Pc(OR-1)OR

PF=P(1-OR) or PF=Pc(OR)/[Pc(1-OR)+OR]

P: rate of controls Pc : rate of disease

Etiologic fraction due to interaction was computed according to Walker (3,4)

(1) Etiologic Fraction due to interaction

$$EF(A \times B) = \frac{R(AB) - R(A\overline{B}) - R(B\overline{A}) + R(\overline{AB})}{R(AB)}$$

(2) Etiologic Fraction due to A and B taken together

$$EF(AB) = \frac{R(AB) - R(\overline{AB})}{R(AB)}$$

R indicates attributable risks

A or B indicates that the factor was present

$\overline{A}$ of $\overline{B}$ indicates that the factor was absent

(3) Index of interaction:

$$I = \frac{EF(A \times B)}{EF(AB)}$$

Analyses of data were performed on the AST-486 computer with the EPI-info, Multlr, and the SAS6.03 software.

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Adjustments for interactions among risk factors

(1) Additive Model:

$RRxy = 1+(RRx - 1) + (Rry - 1) = RRx + Rry - 1$

$RRxy = RRx + Rry - 1$	No interaction
$RRxy > RRx + Rry - 1$	Synergestic interaction
$RRxy < RRx + Rry - 1$	Antagonistic interaction

(2) Multiplicative Model

$RRxy = RRx \bullet Rry$

$\ln RRxy = \ln RRx + \ln Rry$

Results

The 200 primary lung cancer cases, ranging in age 18-78 with an average age of 54 years, had a ratio of squamous cell carcinoma to adenocarcinoma cell carcinoma of 1:2.9. The cases and controls were comparable with respect to the matching variables (age, education, ethnic origin, occupational status, and residential area).

1. EF of all risk factors

Single factor logistic regression analysis identified 12 risk factors. EF of spouse smoking had the most pronounced effect in elevating the risk for lung cancer (0.535), whereas EF of oral contraceptive use produced the smallest risk (0.0694) (Table 1). PF values for both risk factors were negative.

2. EF of the interactions between passive smoking from spouse and other risk factors

The largest value of EF came from the interaction between passive smoking from spouse and oral contraceptive use. It was estimated that possibly as much as 90.55% of female lung cancer cases came from combined presence of passive smoking from spouse and oral contraceptive use (Table 2).

3. Interactions between passive smoking from spouse and other risk factors

Interactions between passive smoking from spouse and other risk factors such as taking oral contraceptives, family history of tumour, poor kitchen ventilation, liking for pickles or salted fish, were suggested based on analysis using a multiplicative interaction model. Interactions between passive smoking from spouse and chronic bronchitis /emphysema, history of tuberculosis show additive effect.

Discussion

The results of this investigation show that passive smoking from spouse, bad ventilation in the kitchen, liking for pickles or salted fish, history of chronic bronchitis, family history of tumour, pulmonary tuberculosis, taking oral contraceptives, were significant risk factors for female lung cancer in Guangdong. Passive smoking from spouse increased the risk for lung cancer in females even after adjusting for confounding (5-8).

Family history of tumor, particularly those with family history of lung cancer, was associated with an increase in risk for lung cancer in women (OR=3.6 and 10.0), with an EF of

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0.1156. It also interacted with passive smoking from spouse, giving an index of interaction value of 0.54.

Both single factor analysis and multi-variate analysis showed that the use of oral contraceptives were associated with an increase in risk for lung cancer in women (OR=2.18, 95%CI=1.08-4.45, $p<0.05$). After adjusted for smoking, its OR was 2.26 (95%CI=1.09-4.68, $p<0.05$). EF of oral contraceptives was 0.0694. The association between oral contraceptives and an increased risk for female lung cancer could have important implications for lung cancer in Chinese females, because of the pervasive use of oral contraceptives by women in China. The results of this study also showed strong interactions to exist between chronic bronchitis/emphysema and family history of tumor. Similarly, strong interactions also were shown between tuberculosis and smoke from husbands (index of interaction=0.43).

Acknowledgements

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TABLE 1
EF of every factors of female lung cancer

Risk Factor	Cases	Controls	OR_{M-H}	OR	95%CI	EF	PF
Tuberculosis	19	5	4.09	1.39-12.93	0.0717-0.0758	181	195
Chronic Bronchitis/Emphysema	30	6	5.71	2.18-15.81	0.1238-0.1413	170	194
Oral Contraceptives	27	14	2.06	0.99-4.32	0.0694-0.0748	173	185
Spouse Smoking	157	107	3.14	1.97-5.01	0.5350-1.1507	43	92
Pickled and Cured Food	111	81	1.83	1.20-2.79	0.2516-0.3362	89	119
Ventilation in Kitchen	150	113	2.30	1.45-3.63	0.4322-0.7495	48	83
Family History of Tumor	34	13	3.00	1.46-6.27	0.1156-0.1307	162	186

TABLE 2
EF of the interactions between passive smoking from spouse and risk factors

Risk Factor	A	B	Cases	Controls	EF (AXB)	EF (AB)	I
History of chronic bronchitis/Emphysema	+	+	25	5	-0.1729	0.9165	-0.189
	+	-	5	1			
	-	+	132	103			
	-	-	38	91			
Use of Oral Contraceptives	+	+	23	3	0.8486	0.9372	0.9055
	+	-	28	13			
	-	+	21	13			
	-	-	6	0			
History of Tuberculosis	+	+	15	3	0.4159	0.9133	0.4273
	+	-	28	12			
	-	+	24	14			
	-	-	6	1			
Family History of Tumor	+	+	27	7	0.4840	0.890	0.5438
	+	-	126	101			
	-	+	7	6			
	-	-	36	85			
Ventilation in Kitchen	+	+	122	63	0.4785	0.8279	0.5779
	+	-	30	53			
	-	+	35	45			
	-	-	13	39			
Diet of Pickled and Cured Food	+	+	90	47	0.3456	0.7840	0.4408
	+	-	20	34			
	-	+	66	61			
	-	-	24	58			

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TABLE 3
OR and X^2 test of husband smoking (A) and other factors (B) formed

B	A	X_3	X_1	X_4	X_8	X_{27}	X_{23}
-	-	1.00	1.00	1.00	1.00	1.00	1.00
-	+	3.07	3.12	2.75	2.65	2.61	2.33
+	-	11.97	4.62	2.95	0.76	1.41	1.70
+	+	11.97	11.54	9.11	15.92	4.63	5.81
X^2		41.35	34.37	34.42	36.87	31.42	39.44

P<0.0001

X_1: History of Tuberculosis
X_3: Chronic Bronchitis /Emphysema
X_4: Family History of Tumor
X_8: Use of Oral Contraceptives
X_{23}: Ventilation in Kitchen
X_{27}: Pickled and Cured Food

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Use of Cancer Registry as an Approach to Assess Cancer Risks Associated with Occupation and Industry

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Abstract

Aim: This study explored the use of cancer registration data to assess cancer risks. Using information contained in the Tianjin Cancer Registry (TCR), the risks for lung cancer associated with occupation and with specific industries were assessed. **Methods:** All cancer cases, involving subjects at least 20 years of age and reported during 1981-1987 to the TCR, formed the basis of the study. Using a case-case method, a comparison was made of one type of cancer cases, with all other types of cancer cases. Data were re-coded according to 30 occupations and 27 industries. The individuals employed in the category being investigated constituted the exposed group, and subjects employed in all other categories were considered as the unexposed group. Statistical analysis was performed by unconditional multiple logistic regression. Regression models included parameters such as sex, age and year of cancer diagnosis. **Results**: The results of our studies were consistent with those of previous reports. A systematic analysis, of the association between specific categories of occupation and industry and cancer among men and women registered in the TCR, confirmed that a number of known or suspected occupational cancer risk factors, which were similar to the ones studied in industrialized countries, existed in this population. **Conclusions**: The main advantages of this design are as follows: 1) use of data from a cancer registration that already existed; 2) the approach is easy, fast and less costly for screening real or potential cancer risks; 3) all factors present in the database of the cancer registry could be evaluated; and 4) The way in which cases and the exposed groups were defined could reduce the influence of confounding and other untoward biases.

Key words: cancer, occupation, industry, risk, registration

Introduction

Research on risks associated with certain occupations has historically played an important role in cancer epidemiology and has led to the identification of many environmental carcinogens, with implications both for preventive measures and for elucidating basic mechanisms of carcinogenesis. Occupational exposures have been estimated to contribute to 2-4% of all cancers in industrialized countries [Doll & Peto, 1981]. This figure, however, varies greatly between countries and time periods [Vineis & Simonato, 1991] and is clustered in subgroups of the general population, such as male blue-collar workers, among whom occupational exposures can contribute up to 25% of all cancers [Nicholson, 1984].

To assess the cancer risks associated with specific occupations, a number of study designs could be used. The most common designs were based on analytical methods, such as cohort and case-control studies. Since the risks for some factors are expected to be low, a larger sample size and higher cost were needed to conduct these studies. In the case of cities or regions

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where cancer registries are in existence, the registered data could be used to evaluate the association that may exist between exposure to certain risk factors and cancer incidence, with a limited budget. This paper describes results of a study aimed at exploring the relationship between certain occupations and industries and the risk for lung cancer, using the data from the Tianjin Cancer Registry.

Materials and methods

The Tianjin Cancer Registry (TCR) is a population based registry covering a population of 3.48 million people living in the central urban area of Tianjin. Cancer cases are reported to the Registry by medical doctors, as required by the Tianjin Health Bureau. Unreported cases are periodically identified through review of hospital records, visits to the local committees, and examination of death certificates. Records missing or had unclear information were verified by mail or home visits. The Registry has been included in the two most recent volumes of "Cancer Incidence in Five Continents" [Muir et al, 1987; Parkin et al, 1992].

All cancer cases, involving subjects at least 20 years of age and reported during 1981-1987 to the TCR, formed the basis of the study. Subjects with no information on occupation, or residing outside the city of Tianjin, or employed as farmers, were excluded. A total of 19491 male and 16605 female cancer cases were included in the analysis.

The following parameters were used in the analysis: sex, age (categorized in six categories: 20-35, 35-44, 45-54, 55-64, 65-74, and 75+), year of cancer diagnosis, and main lifetime occupation and workplace. A comparison was made using the case-case method [Siemiatycki, 1991], in which separate analyses were conducted for each cancer, with lung cancer cases being compared with all other cancers (the latter can be considered as controls in a case-control study). In order to control for the potential confounding effects of smoking, a separate analysis was conducted by excluding smoking-related cancer cases (Table 1). Occupations and industries were coded according to criteria used in the 1982 Third Chinese National Census. They were re-coded according to 30 occupations and 27 industries. The numbers of individuals included in each category of occupation and industry are shown in Tables 2 and 3. For each category, subjects employed in a specific occupation or industry were considered as the exposed group, and subjects employed in all other occupation and industries were considered as the unexposed group, as follows: exposed, the occupation to be investigated; unexposed, all occupations except the exposed one; case group, subjects with the cancer to be investigated; control group, subjects of all cancers except the one being investigated.

Statistical analysis was conducted by unconditional multiple logistic regression. Regression models included parameters such as sex, age and year of cancer diagnosis. Ninety-five percent confidence intervals (CIs) were calculated as the exponential of the regression coefficient plus and minus 1.96 times its standard error. The statistical package GLIM was used for the analysis (Payne, 1985).

Results

Table 1 presents the distribution of cases included in the analysis, by sex and site of origin of lesion. Lung cancer was the leading cancer site for both sexes. Table 2 presents the number of cases by sex and occupation. The occupations were grouped into 30 categories. The

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distribution of the number of cases by sex and industries is shown in Table 3. The total number of categories is 27.

For this study, all cancers were individually analyzed, although only the lung cancer results were presented in this paper (Wang et al, 1994, 1995). Among men, being employed as metal processors, toolmakers and machine assemblers, and "other productive workers and laborers" had increased risk of lung cancer. Females in these occupation categories also displayed slightly elevated ORs. In addition, females being employed as service workers, rubber and plastic and paper workers, also had a significant increase in the risk for lung cancer. No confounding effect of smoking on these associations was suggested, based on analysis excluding smoking related cancers from the controls. Among the industries found to elevate risk of lung cancer were: wood, pharmaceutical and metallurgical industries in males, and production of machinery and transportation equipment and electric and precision instrument among females. Employment in the construction industry increased the risk for lung cancer in both sexes. When non-manual workers were excluded from the analysis, the same results based on industries were obtained; an exception being the risk of male construction workers (OR, 1.14; 95% CI, 0.93-1.41) and of female electric and precision instrument workers. No major changes were found in the results by industry when smoking-related cancers were excluded from the controls (Tables 4 and 5).

Discussion

This study was based on a broad series of comparisons between one type of neoplasm, i.e., lung cancer, and cases of all other cancers. In interpreting the results, advantages and limitations of this type of analysis should be considered.

The study covered the whole range of cancer cases from Tianjin: therefore selection of cases according to social or economic factors, which may operate in hospital-based studies of cancer cases, is not likely to have occurred. In addition, since the comparisons were made across the broad spectrum of cancers, the possibility of spurious results will probably be reduced, given the likelihood that the same selection factors would apply to cases of all types of cancer. Although the fraction of cancer cases not recorded by the registry is unknown, it is likely that this fraction is smaller than in most case-control studies. The fact that both cases and controls came from the same registry also tends to reduce any such bias.

The very large sample size, due to the large population covered by the TCR, gives stable risk estimates. In addition, any confounding effect of tobacco smoking was partially controlled for by excluding smoking-related cancers from all cancers used as controls. It does not seem, however, that, except for a few cancers, smoking had an important confounding effect. Furthermore, the analysis restricted to manual workers should have partially controlled for the confounding effect of smoking as well as that of other factors related to social class or socioeconomic status.

The major limitation of the study is the quality of the information on the occupation and industry of employment. This information is derived from a standardized form used to register cancer cases in the TCR, and is usually provided by attending physicians or hospital clerks. In addition, no attempt was made to obtain the entire occupational history of the cancer cases.

Although it is likely that there will be some misclassification of occupation and industry in these data, it is unlikely that misclassifications lead to differential effects (i.e., cases of one

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cancer types employed in one or more occupations being more (or less) likely to be misclassified than cases of other cancer types). In such a situation, the effect of misclassification in an analysis based on a dichotomous exposure variable would have been to reduce any real association, and not to produce false positive results. It is therefore likely that some real associations have failed to be detected in the present analysis, due to the dilution of the truly exposed individuals in a much larger occupational or industrial category, as well as to the classification of the exposed subjects in several different categories, used as either "exposed" or "unexposed" in subsequent analyses.

Some of the "statistically significant" associations between a given cancer and an occupational group may have been due to chance, particular when the series of cases is based on few individuals. This is a consequence of the many combinations tested in the analysis for all cancers. The results reported in this paper are only for lung cancer.

In addition to unconditional logistic regression analysis that was used in this paper, the poisson regression could have been used to analyze the registered data. When compared to logistic regression, the poisson regression method requires that the data of cases and the data of population be perfectly compatible. For a long term program of cancer registration, such a requirement will be difficult to attain, since coding of factors, e.g., occupation, training of clerk, classification, etc., may vary depending on the personnel composition and their qualification at different periods of time the registry is operative. Due to non-compatibility between the cases data of the TCR and the population data of census, the results of poisson regression analysis would be difficult to interpret. Thus, for data set derived from a disease registry, use of logistic regression is more flexible and efficient than the poisson regression method.

In conclusion, the main advantages of this design are as follows: (i) use of data of a cancer registration that already exists; (ii) it is easy, fast and less costly for screening potential cancer risk; (iii) all factors in the database of cancer registration could be evaluated, for example, by occupation, industry, education, etc.; and (iv) cases and exposed groups are less influenced by confounding and bias.

The results of this study are consistent with those previously reported. The systematic analysis of the association between occupation and industry of employment and cancer among men and women registered in the TCR provided confirmation that in this population a number of known or suspected occupational cancer risk factors existed, similar to what has been reported in other studies in industrialized countries. Other possible occupational risks have been identified in both men and women, which can be addressed by more specific investigations in the future. For the purpose of screening potentially hazardous occupations and industries, the research method used here has broad applications.

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TABLE 1
Cases of cancer included in the analysis, by sex and site of origin of the lesion

Site (ICD-9 Code)	Males	Females	Total
Malignant neoplasm of lip (140*)	17	2	19
Malignant neoplasm of tongue (141*)	51	49	100
Malignant neoplasm of major salivary glands (142*)	39	38	77
Malignant neoplasm of gum (143*)	38	14	52
Malignant neoplasm of floor of mouth (144*)	7	7	14
Malignant neoplasm of other and unspecified parts of mouth (145*)	41	33	74
Malignant neoplasm of oropharynx (146*)	39	43	82
Malignant neoplasm of nasopharynx (147*)	180	83	263
Malignant neoplasm of hypopharynx (148*)	26	16	42
Malignant neoplasm of other and ill-defined sites within the lip, oral cavity and pharynx (149*)	6	2	8
Malignant neoplasm of esophagus (150*)	1756	955	2711
Malignant neoplasm of stomach (151)	3732	1503	5235
Malignant neoplasm of small intestine (152)	57	41	98
Malignant neoplasm of colon (153)	488	493	981
Malignant neoplasm of rectum (154)	631	645	1276
Malignant neoplasm of liver and intrahepatic bile duct (155)	2689	1014	3703
Malignant neoplasm of gallbladder (156)	214	176	190
Malignant neoplasm of pancreas (157*)	555	364	919
Malignant neoplasm of retroperitoneum and peritoneum (158)	44	48	92
Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum (159)	80	70	150
Malignant neoplasm of nasal cavities (160)	86	56	142
Malignant neoplasm of larynx (161*)	325	189	514
Malignant neoplasm of trachea, bronchus and lung (162*)	4806	3595	8401
Malignant neoplasm of pleura (163)	17	26	43
Malignant neoplasm of thymus, heart and mediatinum (164)	56	64	120
Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs (165)	6	13	19
Malignant neoplasm of bone and articular cartilage (170)	197	169	366
Malignant neoplasm of connective and other soft tissue (171)	140	97	237
Malignant melanoma of skin (172)	38	36	74
Other malignant neoplasm of skin (173)	114	87	201
Malignant neoplasm of female breast (174)	-	2407	2407
Malignant neoplasm of male breast (175)	25	-	25
Malignant neoplasm of uterus, part unspecified (179)	-	30	30
Malignant neoplasm of cervix uteri (180)	-	1141	1141
Malignant neoplasm of placenta (181)	-	92	92
Malignant neoplasm of body of uterus (182)	-	353	353
Malignant neoplasm of ovary (183)	-	519	519
Malignant neoplasm of other and unspecified female genital organs (184)	-	72	72
Malignant neoplasm of prostate (185)	108	-	108
Malignant neoplasm of testis (186)	59	-	59
Malignant neoplasm of penis and other male genital organs (187)	76	-	76
Malignant neoplasm of bladder (188*)	666	209	875
Malignant neoplasm of kidney and other and unspecified urinary organs (189)	247	141	388

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Malignant neoplasm of eye (190)	8	16	24
Malignant neoplasm of brain (191)	380	340	720
Malignant neoplasm of other and unspecified parts of nervous system (192)	35	27	62
Malignant neoplasm of thyroid gland (193)	76	213	289
Malignant neoplasm of other endocrine glands (194)	33	34	67
Malignant neoplasm of other and ill-defined sites (195)	2	4	6
Secondary and unspecified malignant neoplasm of lymph nodes (196)	114	98	212
Secondary malignant neoplasm of respiratory and digestive systems (197)	40	38	78
Secondary malignant neoplasm of other specified sites (198)	87	70	157
Malignant neoplasm without specification of site (199)	53	57	110
Lymphosarcoma and reticulosarcoma (200)	181	112	293
Hodgkin's disease (201)	43	35	78
Other malignant neoplasm of lymphoid and histiocytic tissue (202)	295	276	571
Multiple myeloma (203)	62	30	92
Lymphoid leukemia (204)	51	40	91
Myeloid leukemia (205)	165	132	297
Monocytic leukemia (206)	28	28	56
Other specified leukemia (207)	36	35	71
Leukemia of unspecified cell type (208)	146	128	274
TOTAL	19491	16605	36096

(*)smoking related sites

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TABLE 2
Number of cases of cancer, by occupation

Occupation	Male	Female	Total
Professional, clerk, sales worker	6935	2329	9264
Service worker	1120	612	1732
Cook	385	140	525
Miner, quarryman, well driller	46	11	57
Metal processor	375	89	464
Chemical processor and related occupations	207	147	354
Rubber and plastic product worker	208	192	400
Spinner, weaver, knitter, textile dyer	705	884	1589
Leather and fur worker	110	102	212
Tailor, dressmaker, sewer	162	343	505
Food and beverage worker	249	161	410
Tobacco worker	32	36	68
Wood preparation worker	361	63	424
Paper worker	107	102	209
Printer and related occupations	80	34	114
Stone cutter and carver	15	6	21
Blacksmith, toolmaker and machine assembler	1009	436	1445
Machinery fitter, precision instrument maker	518	210	728
Electrical and electronic worker	536	262	798
Broadcasting and sound equipment operator	10	5	15
Plumber, welder and related occupation	169	46	215

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Potter and glass worker	89	42	131
Painter	110	65	175
Bricklayer, carpenter	517	63	580
Stationary engine operator	269	23	292
Material handling and equipment operator	784	53	837
Transport equipment operator	792	43	835
Checking measure testing and laboratory worker	140	166	306
Other productive worker and laborer	1032	491	1523
Unemployed	2419	9449	11868

TABLE 3
Number of cases of cancer, by industry

Industry	Males	Females	Total
Mining	20	13	33
Electric power, steam and hot water	147	24	171
Gas	14	8	22
Water supply	52	8	60
Food, beverage and tobacco	580	286	866
Textile	1510	1105	2615
Leather and fur	484	617	1101
Wood process, furniture	270	73	343
Paper, stationary and printing	515	340	855
Chemistry	494	214	708
Pharmaceutics	120	70	190
Rubber and plastic products	421	262	683
Mineral oil and coal products	232	33	265
Non-metal mineral products	407	150	557
Metallurgy	578	98	676
Metal products	776	382	1158
Machinery and transportation equipment	1576	553	2129
Electric, electronic and precision instruments	1021	649	1670
Other productive and repair industries	425	156	581
Construction	734	98	832
Transportation	1753	157	1910
Post and telecommunications	101	26	127
Commerce	1777	552	2329
Restaurant	321	115	436
Public utilities and residential service	812	215	1027
Health, education, financial, government	2795	1327	4122
Unemployed	1556	9074	10630

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TABLE 4
Malignant neoplasm of trachea, bronchus and lung (ICD 9 : 162)

Occupation	Male				Female			
	case	control	OR	95%C.I.	case	control	OR	95%C.I.
Professional, clerk, sales worker	1714	5221	0.97	0.91-1.04	342	1987	0.74	0.65-0.85
Service worker	282	838	1.02	0.89-1.17	146	466	1.25	0.13-1.52
Cook	88	297	0.87	0.69-1.11	31	109	1.15	0.76-1.73
Miner, quarryman, well driller	8	38	0.70	0.32-1.51	2	9	1.51	0.31-7.38
Metal processor	108	267	1.31	1.04-1.65	17	72	1.13	0.66-1.96
Chemical processor and related	50	157	0.96	0.69-1.32	23	124	0.97	0.61-1.54
Rubber and plastic product worker	48	160	0.92	0.67-1.28	49	143	1.36	0.98-1.91
Spinner, weaver, knitter, dyer	171	534	0.97	0.82-1.16	181	703	1.03	0.87-1.22
Leather and fur worker	23	87	0.79	0.50-1.25	24	78	1.20	0.75-1.92
Tailor, dressmaker, sewer	33	129	0.79	0.54-1.16	78	265	1.16	0.89-1.50
Food and coverage worker	65	184	1.07	0.81-1.43	28	133	0.82	0.54-1.25
Tobacco worker	9	23	1.13	0.52-2.44	8	28	0.94	0.43-2.06
Wood preparation worker	83	279	0.90	0.70-1.15	11	52	0.89	0.46-1.72
Paper worker	22	85	0.81	0.51-1.31	29	73	1.64	1.05-2.56
Printer and related occupations	20	60	1.07	0.64-1.78	9	25	1.50	0.68-3.29
Stone cutter and carver	6	9	2.02	0.71-5.69	2	4	2.49	0.41-15.28
Blacksmith, tool maker	267	742	1.15	1.00-1.33	82	354	1.15	0.89-1.48
Machinery fitter, Prec. M. maker	129	389	1.06	0.87-1.31	36	174	1.02	0.71-1.49
Electrical and electronic worker	110	426	0.86	0.69-1.06	51	211	1.14	0.83-1.57
Broadcasting and sound eq. Ope.	2	8	0.92	0.19-4.45	1	4	2.50	0.27-23.56
Plumber, welder and related occ.	37	132	0.93	0.64-1.34	8	38	1.07	0.49-2.33
Potter and glass worker	27	62	1.38	0.87-2.18	7	35	0.82	0.36-1.87
Painter	32	78	1.23	0.81-1.86	13	52	1.04	0.56-1.93
Bricklayer, carpenter	138	379	1.16	0.95-1.42	11	52	1.21	0.61-2.37
Stationary engine operator	73	196	1.13	0.86-1.48	3	20	0.78	0.23-2.71
Material handling and equip. op.	200	584	1.03	0.88-1.22	10	43	1.18	0.58-2.40
Transport equipment operator	178	614	0.93	0.78-1.10	6	37	0.88	0.36-2.12
Checking testing and lab worker	32	108	0.95	0.64-1.42	24	142	0.81	0.52-1.26
Other productive worker	272	760	1.15	0.99-1.33	93	398	1.14	0.90-1.45
Unemployed	579	1840	0.93	0.84-1.03	2270	7179	1.00	0.91-1.09

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TABLE 5
Malignant neoplasm of trachea, bronchus and lung (ICD 9 : 162)

Industry	Male				Female			
	case	control	OR	95%C.I.	case	control	OR	95%C.I.
Mining	3	17	0.59	0.17-2.03	2	11	1.52	0.32-7.19
Electric power, steam and hot water	38	109	1.13	0.78-1.64	3	21	0.75	0.22-2.59
Gas	2	12	0.52	0.12-2.31	0	8	-	
Water supply	15	37	1.20	0.66-2.19	1	7	1.03	0.11-9.23
Food, coverage and tobacco	148	432	1.02	0.85-1.24	59	227	0.99	0.74-1.33
Textile	339	1171	0.86	0.76-0.97	226	879	1.01	0.86-1.18
Leather and fur	124	360	1.02	0.83-1.25	121	496	0.93	0.76-1.14
Wood process, furniture	78	192	1.24	0.95-1.62	13	60	1.06	0.57-1.98
Paper, stationary and printing	129	386	1.03	0.84-1.26	71	269	1.06	0.81-1.39
Chemistry	120	374	0.99	0.80-1.22	29	185	0.71	0.48-1.07
Pharmaceutics	38	82	1.38	0.93-2.03	14	56	1.11	0.61-2.03
Rubber and plastic products	109	312	1.09	0.87-1.36	59	203	1.18	0.87-1.59
Mineral oil and coal products	55	177	0.96	0.71-1.30	6	27	1.04	0.42-2.58
Non-metal mineral products	106	301	1.07	0.86-1.35	36	114	1.46	0.99-2.15
Metallurgy	166	412	1.28	1.06-1.54	15	83	0.83	0.47-1.46
Metal products	203	573	1.10	0.93-1.30	74	308	1.07	0.82-1.39
Machinery and transp. equip.	398	1178	1.04	0.93-1.18	110	443	1.25	1.00-1.56
Electric, electonic, p. instru.	244	777	0.99	0.85-1.15	139	510	1.23	1.01-1.49
Other productive and repair	103	322	0.99	0.79-1.24	34	122	1.29	0.87-1.90
Construction	199	535	1.21	1.02-1.43	19	79	1.63	0.96-2.77
Transportation	428	1325	0.97	0.86-1.09	29	128	1.13	0.75-1.72
Post and telecommunications	21	80	0.84	0.52-1.36	5	21	1.39	0.51-3.79
Commerce	446	1331	1.00	0.89-1.12	91	461	0.88	0.70-1.11
Restaurant	82	239	1.03	0.80-1.33	31	84	1.39	0.91-2.12
Public utilities and res. service	185	627	0.89	0.75-1.06	49	166	1.32	0.95-1.84
Health, edu. Financ. Govern.	683	2112	0.98	0.89-1.08	191	1136	0.71	0.60-0.83
Unemployed	344	1212	0.87	0.76-0.98	2168	6906	0.99	0.90-1.07

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Risk Factors of Lung Cancer from a Cohort Study in Nagoya, Japan

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Summary

A population-based cohort study on the relationships between various environmental factors and lung cancer risk has been conducted in Nagoya, Japan involving 24,489 inhabitants aged 40 or more. The baseline survey was conducted in 1985 using a self recorded questionnaire. From a 10 year follow-up study, 161 cases with a newly diagnosed lung cancer (120 male cases and 41 female cases) were identified. The various environmental factors at baseline were related to the subsequent risk of lung cancer incidence. The causal relationship between smoking and lung cancer was conformed (RR=5.72; 95%CI=2.50-13.08 for current male smokers and RR=2.05; 95%CI=0.97-4.32 for current female smokers), but relative risks for other various environmental factors were not statistically significant except increased risk for frequent coffee drinking in males (aRR [adjusted for other risk factors]=2.02; 95%CI=1.34-3.05) and decreased risk for frequent intake of green yellow vegetables in females (aRR=0.47; 95%CI=0.23-0.94).

Introduction

From many previous epidemiological studies a number of environmental factors; smoking, occupation, air pollution, indoor air pollution due to heating, cooking, incense burning and others, passive smoking, radiation, diet, etc., were reported as risk factors of lung cancer. However, except smoking and some occupational factors, a causal relationship has not been well established yet. Because of past severe air pollution and recent increase of automobiles in Japan, people and officers at the Environment Agency were concerned about effects of air pollution on lung cancer and some other respiratory diseases. Thus, in 1983 the Japanese Environment Agency started a nation-wide large scale population-based cohort study on various environmental factors and lung cancer involving 3 prefectures (3 relatively heavily polluted areas and 6 less polluted control areas). The follow-up study is still ongoing and the final analysis is planned after completing a 15 year follow-up study in around 2000. This report presents intermediate results on various risk factors of lung cancer based on 10 year follow-up study of one study area in Nagoya, Japan.

Subjects and methods

A population-based cohort study on the relationships between various environmental factors and cancer, especially lung cancer has been conducted since 1985 for the inhabitants aged 40 or more in one urban area (Chikusa-ward) of Nagoya, Japan. The baseline information was obtained by using a self recorded questionnaire. The total number of respondents was 24,489 (10,052 males and 11,476 females) with a response rate of 87.9%. Of all the respondents, 1,591 respondents with unknown history of smoking and those over 80 years were excluded from the

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analysis. Thus, 19,937 respondents (9,616 males and 10,321 females) aged 40-79 years comprised the subjects of the present study.

The follow-up study was based on a municipal transfer record, vital statistics and population-based cancer registry in Aichi Prefecture covering this study area.

The statistical analyses were conducted by using the SAS program. The multivariate analysis was conducted by using the Cox regression analysis.

Results

1) The follow-up results

During the 10 year follow-up study, 1,045 (5.2%, 596 males and 449 females) died and 4,645 (23.3%, 2,395 males and 2,250 females) moved out from the study area. A total of 161 cases with a newly diagnosed lung cancer (120 male cases and 41 female cases) were identified from the follow-up study.

2) Smoking rate

The smoking rate at baseline was 54% in males and 13% in females. The percentage of ex-smokers was 30% in males and 5% in females with the percentage of ever-smokers being 84% in males and 18% in females.

3) Relative risks of lung cancer for smoking habit

The age-adjusted relative risk (RR) and its 95% confidence intervals (CI) of lung cancer for smoking habit were shown in Table 1. The RR was significantly greater for male current smokers (RR=5.72, CI=2.50-13.08) and those who smoked more than 40 years. The RR was higher for heavy smokers and those who started smoking at younger ages.

4) Relative risks of lung cancer for passive smoking

The age-adjusted RR and its 95% CI of lung cancer for passive smoking were shown in Table 2. The RRs for men with passive smoking from smoking parents in childhood and smoking household members were greater than2, but none of them were statistically significant.

5) Relative risks of lung cancer for occupation, heating and pets in the room

The age and smoking-adjusted RR and its 95% CI of lung cancer for occupational exposure to fine particles and gasses, indoor heating system and having pets in the room were shown in Table 3. None of the RRs were statistically significant.

6) Relative risks of lung cancer for selected food and drinks

The age and smoking-adjusted RR and its 95% CI of lung cancer for some selected food (green-yellow vegetables and fruits) and some drinks (green tea, coffee and alcohol) were shown in Table 4. Male coffee drinkers showed slightly increased risk of lung cancer, but the same trend was not observed in female coffee drinkers. Separate analyses were done for coffee drinking according to smoking habit in males and the increased risk was more markedly observed in never-smokers. The increased risk remained in a multivariate analysis after adjusting for other

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potential confounding factors. The RR was significantly reduced in ex-drinkers and insignificantly reduced in other categories of drinkers only in males.

None of the RRs for other dietary and drinking habits were statistically significant.

7) Results of a multivariate analysis

The adjusted relative risks (aRR) and 95%CI of lung cancer for smoking, indoor heating system, green tea, coffee, green yellow vegetables, fruits and alcohol drinking were shown in Table 5. Smoking an coffee drinking were independent risk factors of lung cancer in males and frequent intake of green yellow vegetables was an independent protective factor for lung cancer in females. An adjusted relative risk for those using stove without exhaust pipe was significantly reduced only in males.

Discussion

The main aim of the present nation-wide population-based cohort study on various environmental factors and lung cancer was to evaluate the effects of air pollution on lung cancer after adjusting for all possible confounding factors and also to identify any new environmental risk factors for lung cancer. The study areas were selected from surrounding areas of the national air monitoring stations where all kinds of particulate and gaseous air pollutants had been monitored for a long time. The effects of air pollution on lung cancer will be studied by relating the levels of air pollution for various pollutants to the mortality and incidence rates of lung cancer after adjusting for other risk factors of lung cancer. These analyses will be conducted after the 15 year follow-up study is completed in all study areas. Thus, in the present study in one area alone effects of air pollution could not be studied.

In the present study the causal relationship between smoking and lung cancer was confirmed. But for other various environmental factors, except an increased risk for male coffee drinking and decreased risks for frequent intake of green yellow vegetables and those using stove without exhaust pipe, RR of lung cancer were not statistically different from unity. There may two major reasons for this. One possibility is that those risk factors are all weak risk factors and easily confounded by other strong risk factors. Another more important possibility is that because of a small number of study subjects/events and a short follow-up period the statistical power is too weak in the present study to detect effects of weak risk factors with a relative risk close to unity; 0.07-1.30.

The final analyses for each study area and pooled data sets of all study areas will be conducted in the future after completing the 15 year follow-up and we may be able to find some other significant risk factors of lung cancer then. The effect of air pollution on lung cancer risk will also be studied after completing the 15 year follow-up and analyzing data from all the 9 study areas.

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TABLE 1
Age-adjusted relative risks (RR) and 95% confidence intervals (95%CI) of lung cancer for smoking

Smoking habit	Males		Females	
	Events	RR(95%CI)	Events	RR(95%CI)
Smoking status				
Never smokers	6	1.00	30	1.00
Ex-smokers	19	1.39 (0.56-3.48)	2	1.05 (0.25-4.39)
Current smokers	95	5.72 (2.50-13.08)	9	2.05 (0.97-4.32)
Years of smoking				
1-39 years	34	1.85 (0.76-4.50)	6	1.20 (0.50-2.88)
40+ years	80	6.44 (2.72-15.23)	4	4.02 (1.36-11.9)
No. of cigarettes/day				
1-19	34	2.81 (1.18-6.72)	7	1.63 (0.72-3.71)
20-39	65	4.37 (1.89-10.11)	3	1.80 (0.55-5.91)
40+	16	4.08 (1.57-10.58)	1	6.68 (0.90-49.4)

TABLE 2
Age-adjusted relative risks (RR) and 95% confidence intervals (95%CI) of lung cancer for passive smoking among never-smokers

Passive smoking	Males		Females	
	Events	RR (95%CI)	Events	RR (95%CI)
Passive smoking from smoking parents in childhood				
No	1	1.00	9	1.00
Yes	4	2.36 (0.26-21.24)	19	0.81 (0.37-1.79)
Passive smoking from current smoking household members				
No	3	1.00	11	1.00
Yes	2	2.49 (0.41-15.06)	17	1.69 (0.79-3.62)

TABLE 3
Age and smoking-adjusted relative risks (RR) and 95% confidence intervals (95%CI) of lung cancer for occupational exposure to fine particles and gasses, indoor heating system and having pets in the room

Exposure resources	Males		Females	
	Events	RR (95%CI)	Events	RR (95%CI)
Occupational exposure to fine particles and gasses				
No	71	1.00	35	1.00
Yes	45	0.91 (0.63-1.32)	4	0.57 (0.20-1.63)
Indoor heating system				
Electric or "clean heating" system	56	1.00	17	1.00
Stoves without exhaust pipe	64	0.91 (0.63-1.32)	23	0.89 (0.48-1.67)
Pets in the room				
No	102	1.00	34	1.00
Yes	17	0.72 (0.43-1.20)	6	0.71 (0.30-1.69)

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TABLE 4
Age and smoking-adjusted relative risks (RR) and 95% confidence intervals (95%CI) of lung cancer for some selected food and drinks

Food/drinks	Males		Females	
	Events	RR (95%CI)	Events	RR (95%CI)
Green yellow vegetables				
≤2 times/week	39	1.00	7	1.00
3-4 times/week	34	0.83 (0.52-1.30)	19	1.73 (0.72-4.13)
Every day	46	0.69 (0.45-1.05)	15	0.89 (0.36-2.20)
Fruits				
≤2 times/week	30	1.00	5	1.00
3-4 times/week	33	1.21 (0.74-1.98)	10	1.54 (0.52-4.58)
Every day	53	0.83 (0.53-1.30)	26	1.42 (0.53-3.79)
Green tea				
≤2 cups/day	30	1.00	7	1.00
3-4 cups/day	33	0.93 (0.57-1.52)	11	1.13 (0.44-2.92)
+5 cups/day	43	1.08 (0.68-1.73)	20	1.69 (0.71-4.01)
Coffee				
<sometimes	30	1.00	5	1.00
sometimes	27	0.98 (0.50-1.90)	18	1.27 (0.59-2.71)
1-2 cups/day	58	1.85 (1.00-3.42)	10	0.74 (0.29-1.86)
3+ cups/day	21	1.89 (0.91-3.91)	2	0.49 (0.09-2.56)
Alcohol drinking				
Almost never	29	1.00	22	1.00
Quit	6	0.35 (0.14-0.84)	2	1.58 (0.35-7.23)
Sometimes	31	0.67 (0.40-1.10)	12	1.06 (0.51-2.20)
Every day				
<2 drinks	25	0.61 (0.36-1.06)	0	-
≥2 drinks	26	0.75 (0.43-1.30)	0	-

TABLE 5
Adjusted relative risks (aRR) and 95% confidence intervals (95%CI) of lung cancer for smoking and some selected food and drinks by using a Cox regression analysis

Factors (categories)	Males aRR (95%CI)	Females aRR (95%CI)
Smoking (current/ex-vs. never)	3.20 (1.39-7.35)	1.96 (0.90-4.26)
Indoor heating system (stoves without exhaust pipe vs. others)	0.64 (0.44-0.93)	1.11 (0.56-2.19)
Green tea (5+ cups vs. less)	1.29 (0.88-1.90)	1.54 (0.79-2.98)
Coffee (everyday vs. less)	2.02 (1.34-3.05)	0.92 (0.44-1.93)
Green yellow vegetables (everyday vs. less)	0.80 (0.54-1.20)	0.47 (0.23-0.94)
Fruits (everyday vs. less)	0.86 (0.58-1.28)	1.28 (0.63-2.60)
Alcohol drinking (current/ex- vs. never)	0.67 (0.43-1.04)	0.87 (0.43-1.76)

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Biological Factors as Confounders for Chemical Agents

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Introduction

Investigations on risk factors are an important part of the scientific efforts to assess the relation between the environment and risk for disease. Risk assessment has a long tradition in mankind. Already around 3200 BC, the Sumerians had special priests - the Asipus - whose role was to evaluate risks. In that society, they helped kings, governors or individuals to evaluate risks, using a simple mathematical system in terms of "yes" or "no". The sum of these directed the actions in marriage, buying property or other everyday events in the society.

Today, risk estimations are just as important as during Sumerian times and the results are still expressed as numbers. The priests of today as epidemiologists, statisticians and toxicologists. The procedures to arrive at the numbers for risk, however, become very complicated.

A major component in this complexity is that our risk estimations now deal with low numbers. Most, if not all, of the large risks related to environmental agents have been defined and described. In the conquest for health, our attention is thus increasingly directed towards low risk agents.

Two questions of particular importance in the risk evaluation today are the simultaneous presence of low risk and high risk agents and the problem of confounders in terms of natural exposures. Research during recent years has demonstrated that these issues may be combined into a very potent source of error, namely the attention paid to low risk chemical agents when high risk biological agents are confounders. In the following this issue will be discussed and illustrated with examples from current research. Initially I will deal with some basic objectives for environmental epidemiology and conclude with aspects on the responsibility of the researcher.

Objectives for environmental epidemiology

The objectives of epidemiological studies on the effects of environmental agents have been defined by WHO [1983]. These objectives are given in Table 1.

In addition to the objectives as listed by WHO, environmental epidemiologists also have a responsibility to provide information to the society, including the public. Epidemiological numbers on risks are relatively easy to visualize, compared to data from toxicological or in vitro tests but the interpretation of the significance for human health is sometimes difficult, particularly for low risk agents.

Basic considerations

1. High and low risk agents

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Environmental agents can represent a high or a low risk for a certain disease. The relative magnitude may vary according to circumstances - radon which is a low risk agent for lung cancer in the population, is a high risk among workers in mines.

Obviously it is important to describe the exposure to the high risk agent with a high precision before analytical work on the low risk agent is undertaken. This is particularly important if there is a correlation the low and high risk agents. The concept is illustrated in Figure 1.

It is seen from the figure that the variation in exposure estimate at a high risk may alter the risk but it remains elevated. At the low risk level, the same magnitude of exposure variation can cause a risk to be present or absent.

2. Biological agents

By tradition we are led to believe that chemical agents in the environment are the most potent inducers of effects. During the last year it has become apparent that natural or biological agents or lack of these can be just as harmful, if not more harmful to man. As several of these vary with chemical exposures, they act as confounders in epidemiological studies. Furthermore some of them have only been detected during the last years, thus affecting the conclusions from previous studies where they have not been controlled for.

3. Examples

The traditional risk factors for lung cancer are inhaled combustion products, radon and occupational exposure. These are high risk factors. However in a study on non-smoking females from the US, it was shown that consumption of saturated fat was a high risk factor for lung cancer [Alavanja et al. 1993]. This is illustrated in Figure 2.

It is seen that the odds ratio for lung cancer was around 6 in the group with the highest consumption of saturated fat. This finding has been verified in a subsequent study and supportive data come from previous studies which show that fat is a risk factor for cancer [Goodman et al. 1988; Hinds et al. 1983; Kolonel et al. 1981]

The immediate consequences of the findings as reported in Figure 2, are of course that fat must be considered as a risk exposure in all studies on lung cancer and that no conclusions can be drawn regarding lower risk factors, if fat consumption has not been controlled for.

Another consequence of the Alavanja study relates to truck drivers. A slightly increased risk for lung cancer and cardiovascular disease has been described for this occupation. A common interpretation is that these effects are caused by exposure to diesel exhaust. In view of the findings on fat and lung cancer, it can be hypothesized that the increased disease risks are not due to the relatively low risk agent diesel exhaust but rather to a high risk diet containing high fat foods at the cafeterias during night shifts. Not until this factor has been controlled for, can a final evaluation of the previous hypothesis be made.

Yet another example on the importance of high risk agents for confounding is as follows. To assess the possible relation between exposure to environmental tobacco smoke (ETS) and disease, non-smoking females living with smoking or non-smoking partners have been studied and in some of these studies, an increased risk has been found. However, it is well known that smokers have a diet that is different from non-smokers [Morabia and Wynder 1990, Subar et al.

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1990, Thompson and Warburton 1992]. Some of these differences, e.g., the consumption of fried food or a low consumption of vegetables, relate to an increased risk for disease [for a review see Block et al. 1992].

Consequently studies have been performed where dietary habits of non-smokers living with nonsmokers or smokers have been compared [Koo et al. 1988; Sydney et al. 1989; Cress et al. 1994; Matanoski et al. 1995]. The results from one such study, performed on populations in Sweden and Switzerland [Rylander et al. 1997], are shown in Figure 3.

It is seen that the risk to find a smoking partner was higher among females consuming vegetables and fiber rich food more seldom. A low consumption of vegetables and fibers is a risk factor for disease. A low consumption of vegetables and fibers is a risk factor for disease. Risks for disease related to living with a smoker might thus be influenced by dietary habits and not necessarily by the exposure to the chemical agents ETS.

A further example of the need to control for the major risk factor can be taken from another study on ETS. A relationship between ETS exposure and cardiovascular disease has been found in some epidemiological studies. Several of these have not been controlled for one important high risk factor for the disease - the food intake. When this factor was controlled for in one of the studies, all odds ratio related statistical significances disappeared [He et al. 1994].

The importance of biological agents in comparison to chemical agents is illustrated in studies on childrens' chest symptoms and indoor exposure. In a number of studies, relationships with indoor chemicals such as volatile organic compounds or products of combustion have been looked for. There is however overwhelming evidence that damp buildings and mold growth is the major factor related to the symptoms [Strachan et al. 1989; Dijstra et al. 1990, Dales et al. 1991]. It has also been shown that a particular agent in molds - the cell wall structure (1 - 3)-β-glucan - alters macrophage function and modifies the response to antigens [Fogelmark et al. 1994; Rylander and Holt 1997]. As poor housing conditions with mold growth covary with other risk factors such as cooking habits, poor ventilation and cigarette smoking by partners, molds act as confounders if the exposure to indoor chemicals is evaluated.

Finally several recent studies show that lack of magnesium is an important risk factor for cardiovascular disease [Rylander 1996, Rubenowitz et al. 1996] and particularly death in heart infarction. A low intake of magnesium is found in persons with poor dietary habits and among persons consuming alcohol regularly. These characteristics are related to chemical environmental exposures such as combustion products and exposure at work. Magnesium can thus act as a confounder and need to be controlled for in studies on cardiovascular disease.

Responsibility of the researcher

The researcher should be aware of the many pitfalls involved in the interpretation of his/her own data. The "wish bias" of the researcher is an important error in the interpretation of results from epidemiological studies [Wynder et al. 1990], particularly when it comes to studies on low risk agents. Adhering to the accepted paradigm - the "paradigm bias" - is another important danger, where the joy of finding data that agree with the paradigm could make the researcher less critical of these data whereas inconsistent data might be pushed aside. As has been pointed out earlier [Koo 1995], inconsistency which challenges the paradigm is probably more valuable and interesting from a scientific point of view.

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For all environmental epidemiological research data, there are difficulties explaining the impact of the data to the public. The information impact of different types of information among researchers and the population is widely different. Whereas an association has a large impact on the public - and should not have it on the scientist - the more advanced means to ascertain a causation such as biological plausibility or the results from intervention studies are not acknowledged to the same degree by the population and may even not be understood.

In studies on high risk factors, it is relatively easy to calculate attributable risk and arrive at a fairly accurate estimate of the impact of a particular environmental factor. Concerning low risk agents, the result obtained becomes very unprecise in view of the low risk number, the proportionally high variation of the confidence interval, and the problems of confounding factors (identified or not). The procedures for reporting the data, their limitations, and the cautions to be taken are an important part of the Good epidemiology practice protocol and it is the responsibility of the researcher to delineate them in detail.

Conclusion

Without precautions established to properly control the many methodological problems present, epidemiology can bring chaos and in the end, a mistrust to public health an environmental medicine, severely delaying the progress in the field of prevention. With prudence, caution and the application of Good epidemiological practice, epidemiology can, in spite of its inherent methodological problems, bring new knowledge to the understanding of disease and environment, with corresponding gains in preventive power and population health.

Acknowledgement

Our own studies on dietary habits and ETS, as well as indoor molds and disease, were supported by grants from the Center for Indoor Air Research (contracts 94-07 and 96-09).

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TABLE 1
Objectives of epidemiological studies of the effects of environmental agents

- Provide decision makers and health workers with information needed for the establishment of health criteria and programs for the control of pollution and other environmental health hazards
- Assist in evaluating the efficacy of preventive and control measures in protecting human health from environmental hazards and to improve quality of life
- Improve scientific knowledge of the effects on health of environmental conditions

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FIGURE 1
Extrapolation of risk for low risk and high risk environmental agents. The variation in exposure determination is indicated by grey zones.

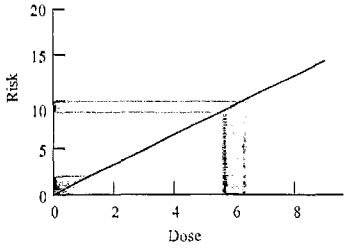


FIGURE 2
Risk for lung cancer among non-smoking females in relation to consumption of saturated fat (Alavanja et al 1993).

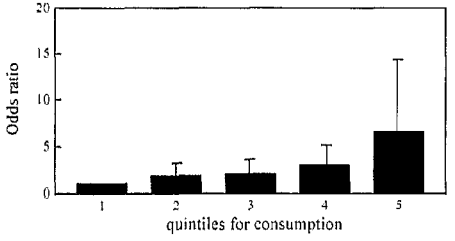
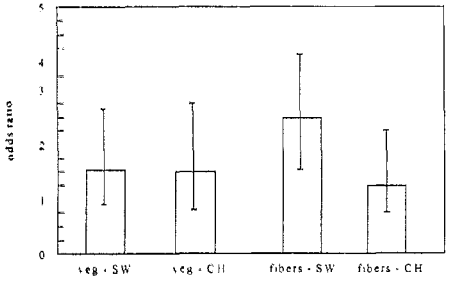


FIGURE 3
Odds ratios for finding smoking partner among non-smoking females with a less frequent consumption of vegetables and fibers.



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Composition of Chinese Diets in Relation to Risk Factors for Human Health

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Introduction

Three kinds of diet are commonly used by people worldwide. The first is a diet rich in animal ingredients but low in plant contents, and is typically represented by the high calorie, high sugar, and high fat food consumed by a relatively large percentage of the population in developed countries. A second type of diet, adequate in calories and rich in plant food ingredients but low in fat and protein contents, is traditionally consumed in developing countries. A third type of diet, characterized by balanced plant and animal ingredients, with sugar, protein and fat contributing almost equally to the total calories, is one considered to be commonly practiced in Japan. It has been advocated as the diet that presumably embodies the desirable features of both Asian and Western foods. As overall economic conditions of countries and people improve, it has been noted that dietary preference tends to shift from the second to the first kind, which translates to a reduction of calories from carbohydrates, with compensatory increases from proteins. Correspondingly, intake of fat becomes much greater. Such a trend is not only found in developed countries, but in developing countries as well.

China is a developing country with more than 20% of the world population. The economic reform started in the 1980s has resulted in better overall living conditions for the population at large. Along with the significant economic improvements, there has been a noticeable shift of people's diet from the second to the first type.

Changes in the composition of Chinese diets

A survey was conducted by the Institute of Nutrition and Health of the Chinese Academy of Preventive Medicine. The survey involved twelve provinces, cities, and self governing regions of China and was aimed at comparing composition of Chinese diets between 1982 to 1990. The results show that there was a consistent drop in intake of proteins derived from plant sources, which was accompanied by a significant increase in intake of animal proteins. Overall, a 10.9% drop in various kinds of consumable foods was observed over the 8-year period, with a 49.9% decrease in carbohydrate intake, and a 81.1% increase in meat consumption, along with a 200% increase in egg consumption, a 323% increase in milk product consumption, and a 97.4% increase in consumption of fish and other seafood products. The overall reduction in calorie intake was 11.3%. However, there was a 13.7% relative increase in the percentage intake of animal proteins, and a 16.1% increase in fat intake. These findings clearly show that the average nutritional intake of Chinese in the year 1990 not only matched the goals and standards set by the World Health Organization, but actually exceeded them. This is especially true in the case of city residents (Table 1). In a subsequent national nutrition survey conducted in 1992, the portion of total caloric intake contributed by fat, in areas whose economic scales range from low, intermediate, to high, was found to be 14.%, 18.2% and 23.7%, respectively, in rural area residents, compared to 23.5%, 30.6% and 33.1%, respectively, for city dwellers. These results show that despite the difference in composition of diets between rural and city residents, the

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overall trend is for the consumption of animal products to increase, which is generally in line with an improvement in overall economic standing. The magnitude of such a trend change is, of course, substantially more significant in city dwellers where diets tend to be more "westernized".

When the Shanghainese diet in 1985 was compared to that of 1950, the most noticeable increases were in the consumption of meat, poultry, seafood, and sugar, whose indices were 281, 492, 291, and 282, respectively. Thus, in 1990, more of the calories come from consumption of animal fat and proteins.

Diet and diseases

Whereas high economic development and industrialization has significantly reduced the incidence of malnutrition and infectious disease, the relatively pervasive poor dietary habits of people living in well developed countries have led to an increase in the incidence of chronic diseases, such as, coronary heart disease, stroke, cancer, diabetes, and many forms of bone diseases. The main culprit is thought to be related to ingestion of high caloric animal products, as well fat, sugar, and salt, added during food processing. Moderate to severe obesity is now becoming commonplace in many countries. In developed countries, coronary heart disease and cancer are the primary causes of death, whereas in developing countries, infectious disease and parasites are responsible for a high percentage of deaths.

In China, infectious disease, which ranked as the first cause of death in the 1950s and 1960s, is now considered to be the ninth cause of death. By contrast, there is a rapid rise in deaths attributable to coronary heart disease and cancer. Tables 2 and 3 show data obtained in the city of Shanghai. Statistical analysis show an inverse correlation between consumption of various types of vegetable/food food groups and mortality due to coronary heart disease (CHD) and cancers. A direct correlation exists between these causes of death and consumption of high caloric and high fat food groups.

Against the background of data presented in Tables 1-3, there are close to a billion people worldwide still failing to meet the minimum requirement for calorie and protein intakes. Likewise, deficiencies in trace elements such as iodine, vitamin A, and iron, are experienced by over 2 billion people. WHO reports that under-nourishment are common in 1.7 billion children under the age of 5 in developing countries, as evidenced by under weight, stunted growth, widespread infections, compromised immune functions, etc., the collective outcome of which is an increase in morbidity and mortality due to infectious and chronic diseases. These problems are also found in many poorly developed regions in inner parts of People's Republic of China.

Conclusions

Two challenges face policy makers and scientists in People's Republic of China. First, there need to be improvement made in nutrition and diet in less well developed parts of China, so as to control "poor men's illness". Secondly, greater emphasis need to be placed to maintaining balanced diets in economically well developed regions of China, so as not to follow the trails of Western cultures.

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TABLE 1
Average daily nutrient intake in Chinese diets compared to WHO standards

	WHO Nutrient Standard*		Median Value in Chinese (1990)
	Lower Limits	Upper Limits	
Total Calories (Kcal)	(see footnote[a])		9.2(2203.3)
Total Fat (% of total calorie)	15.0	30.0[b]	21.2
Saturated Fat (% of total calorie)	0.0	10.0	5.9
Unsaturated Fat	3.0	7.0	5.8
Cholesterol in Diets (mg/d)	0.0	300.0	178.6
Total Carbohydrates (% total calorie)	55.0	75.0	66.1
Complex Carbohydrates (% total calorie)	50.0	70.0	
Fiber (g/d) from Non-Sugar Polysaccharides (NSP)	16.0	24.0	
Total Fiber	27.0	40.0	26.6
Sugar (% total calorie)	0.0	10.0	0.6
Protein (% total calorie)	10.0	15.0	11.6
Salt (g/d)	-	6.0	13.9

*Taken from WHO Technical Report Series No. 797 (1990) Geneva, Switzerland.
[a] Required to maintain normal growth and physiological activity; between 1850-2900 Kcal for an adult.
[b] Temporary goal; ultimate goal being 15%.

TABLE 2
Relation between food groups and diseases

Food Group	Correlation Coefficient		
	Coronary Heart Disease	Cerebral Vascular Disease	Tumor
Carbohydrate	- 0.2009	- 0.4542	- 0.6067
Vegetable	0.0920	0.1142	0.1340
Poultry/Eggs	0.9008	0.8036	0.7461
Meat	0.7892	0.4996	0.4929
Cane Sugar	0.9359	0.8640	0.7891

TABLE 3
Relation between specific nutrients and diseases

$Y = -7.8538 + 4.2654X_1 + 0.2349X_2$
Y: Coronary heart disease's mortality rate ($1/10^5$)
X_1: Saturated fatty acids
X_2: Cholesterol
$Y = 70.7081 + 3.8212X_1 - 21.5971X_2$
Y: Cerebral vascular disease's mortality rate ($1/10^5$)
X_1: Saturated fatty acids
X_2: P/S
$Y = 172.4627 - 0.4627X_1 + 9.3315X_2$
Y: Tumor
X_1: Carbohydrates
X_2: saturated fatty acids

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Drinking Water and Primary Liver Cancer in China

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In China, the distribution of age-adjusted death rates for primary liver cancer (PLC) (1975-1978) show that the highest rates (30/100000) occur in the southeast coastal regions of China, particularly in Fusui, Qidong, Tongan, and Shunde. The geographic distribution of PLC in these locales is not even. Qidong, Haimen, and neighboring counties define a dividing line separating the localities into high- and low-mortality areas, which have been in existence for many years. Moreover the same situation can also be found in Rudong, suburb of Shanghai (Nanhui) and Fusui. All high PLC mortality locales are dependent on a closed-in water system in which the turnover and exchange, i.e., in-flow and out-flow of water is infrequent (1). For the past twenty years, we had hypothesized that the high incidence of PLC may be related to the drinking water system. Evidence in support of a contaminant(s) (which we called H2O +Xi) in the drinking water which may be causally related to the high rates of PLC in these locales was obtained and presented in this paper.

Methods and material

The epidemiological survey of cancer was carried out in China during 1973-1975. Since then we selected some hyperendemic areas to conduct cross-sectional studies on the relationship between drinking water and PLC. These studies were repeated several times by numerous teams of investigators at different periods and in various locations. The data for PLC case-control studies came primarily from two sources: one was a collection of ten raw data sets generated from case-control studies; a second source came from 23 papers published in the Chinese scientific literature between 1980-1993, which was collectively analyzed by meta-analysis.

The laboratory studies were carried out with rats fed either pure Microcystins (MC) or crude Microcystins (MC) isolated from the drinking water from Dianshan Lake. Attempts to remove MC only used raw MC from Dianshan Lake. The genotoxity tests were performed using crude MC. Assays included: the Ames's test, micronucleus assay (MN), replicative DNA synthesis (RDS), and unscheduled DNA synthesis (UDS).

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Results

Cross-sectional studies.

Comparative studies of a number of environmental factors were made in different regions of Qidong-Haimen showing different levels of PLC mortality. The results showed that: 1) the people in lower mortality area (<20/100 000) drink running river water which comes directly from Yangtze river; 2) the people in high mortality area (>100/100 000) drink pond-ditch water which originates from irrigation canals; 3) Within the higher mortality regions, there were localized areas with low PLC mortalities, e.g., Green Islands, with a mortality <10/100 000, where people drink deep well water (200 m underground); 4) Even after adjusting for aflatoxin levels in the diet and the frequency of HBV infection, PLC mortality rates of residents with

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different drinking water sources were still significantly different; 5) When the water sources were primarily deep wells and tap water, the mortality rate of PLC is stable and comparable to the control areas (2).

The association between drinking pond-ditch water with high mortality of PLC has been observed and investigated not only in Qidong, but also in Haimen, Nanhui, Fusui. For example, in Fusui Guangxi, 35.7% of people consume pond water, and the corresponding PLC mortality was 53.12/100 000; however, in a low-mortality area where people typically drink spring and deep well water, mortality only 18.74 and 12.17/100 000, respectively (3).

Meta-analysis.

Twenty-three case-control studies on PLC risk factors in China were published in the Chinese scientific literature. They were analyzed by meta-analysis. The pooled odds ratio (OR) and the population attributable risk (PAR) for HBsAg were 12.61 (95% CI, 10.11-15.74) and 63.91%; for family history of PLC, the calculated values were 4.62 (95% CI 3.39-6.30) and 21.06%; and for drinking pond-ditch water, the numbers were 2.34 (95% CI 1.09-5.02) and 30.39%, respectively (4) (Table 1).

Case-control study.

Changing patterns for PLC risk factors were studied by combining ten case-control studies of PLC. The data from studies performed in Northern and Southern China were separately compiled and analyzed. In Southern China, the following OR and PAR values were obtained: 8.31 and 59.39% for HBsAg, 2.31 and 15.62% for family history of PLC, 1.60 and 18.01% for drinking pond-ditch water, and 0.71 for annual income (all indicators were statistically significant, $P<0.01$). In Northern China the corresponding OR and PAR were as follows: 15.75 and 62.83% for HBsAg, 4.99 and 10% for family history of PLC, 2.82 and 16.15% for history of hepatitis, 1.54 and 14.01% for alcohol drinking respectively ($P<0.01$, based on logistic regression analysis) (5) (Table 2). Interestingly a recent case-control study performed in Haimen did not show significant difference between drinking water sources and PLC cases. Such a result may be explained by improvements in drinking water situations or due to weak associations.

Further analysis indicated that consumption of pond-ditch water and river water have synergistic effect with hepatitis B virus (HBV). When both factors exist, the relative risk increases to 11.67, when compared to HBsAg negative and well water-consuming controls (6).

Studies with F344 rats.

Zhou and Yu (1990) performed a study involving two-stage partially hepatectomized (PH) F344 rats. Rats were injected with AFB1 (50 μg/kg, ip for two weeks) and fed 8 months with water containing heat-evaporated residual material (<60° C) prepared from either pond/ditch or deep well water. After rats were sacrificed, slides were prepared from hepatic tissues and stained with GGT (Gamma-glutamyltransferase) specific antibodies. The intensity of the stain was quantified by an auto-quantitative sereological method. The results showed that the GGT+ foci of (PH+AFB1+Pond/ditch water) group was 2-fold higher than the corresponding value of rats fed (PH+AFB1+deep-well water. The data suggest that pond/ditch water residual may

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contain some carcinogens or promoter substances which could explain the relationship reported to exist between drinking water and liver cancer (7).

MC is a promoter of liver cancer.

In the F344 animal study, it was also observed that although MC injection alone did not produce GST-P positive foci, when combined with DEN or AFB1, MC injection resulted in a dose-dependent increase in GST-P foci in F344 rats. These results support the idea that MC may be a promoter for liver cancer (8).

Identification of suspected substances in water.

Since previous studies showed no relationship between liver cancer and hepatitis virus, aflatoxins, and DDT and BHC in drinking water, we focused on studies of algal toxins because of the heavy pollution of pond/ditch water by algae. In 1992, we collected 65 drinking water samples from Haimen hyper-endemic PLC area. By high performance liquid chromatography/mass spectrometry (LC/MS), two positive identifications of Microcystins (3-desmethyl) were made (9).

By using a highly sensitive indirect competitive ELISA method, which was based on a monoclonal antibody developed by Ueno and coworkers, we showed that: 1) there was seasonal variation of Microcystins (MC) in water, the peak being from June to September; 2) during these months the average concentration of MC in pond/ditch water was 164.9±93.2 pg./ml; for comparison, the MC in irrigated river was 188.7±20.8 pg/ml; 3) the intake of MC was 255.6 ng/day (1.5 liter drinking water/day); 4) the average and highest concentrations of MC in pond/ditch water was 101 and 300 pg/ml; in irrigated river, the values was 160 and 1558 pg/ml respectively (10).

Laboratory procedures to remove MC in the drinking water.

Hypereutrophication usually causes overgrowth of toxic algae species. Experiments were performed to remove the microcystin from untreated water from Dianshan Lake by bleaching powder, alum, activated carbon, resin, maifan stone, ultraviolet ray, boiling and making tea. The results showed that bleaching powder and activated carbon were more effective in removing MC from raw water, and reduced MC by 96.1% and 90.5%, respectively. Resin was less active (88.5%), and alum, maifen stone, and ultraviolet ray were not effective. MC was not remove by boiling tea and tea making (11).

Genotoxicities of MC extracted from lakes (12).

The blooms collected from lakes were washed twice and lyophilized. Ten mg of the lyophilized samples were dissolved in 1 ml water and sonicated in an ultrasonic bath for 5 min. After centrifugation (10 min, 10000g), the supernatant containing the MC was passed through a C18 columns (25 mg dry cell/ml) (RMC). The RMC significantly increased the micronucleus frequency in SHE cells in a dose-response manner. However, RMC did not induce reverse mutagenesis in the TA98 and TA100 assays, with or without the addition of S9 (Table 3).

The effects of RMC on DNA synthesis (RDS) and unscheduled DNA synthesis (UDS) were tested at doses of 1.25, 12.5, 125 g dry cell/ml. The results showed that the toxins could significantly increase the replicate DNA synthesis. However, RMC did not induce an increase in

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UDS (Table 4). These results suggest that RMC may enhance cells proliferation but not DNA damage. In this regard, RMC may be considered as a nongenotoxic substance.

The two-stage transformation assays of SHE cells was employed to identify the promoting activity of RMC (Table 5). The target cells were first exposed to a low dosage of 3-methyl-cholanthrane (MCA) and then to the RMC. The results showed that the RMC could significantly enhance the MCA-initiated cell transformation. However, it failed to induce the SHE cell transformation without pretreatment by MCA. It would appear, therefore, that RMC is a promoter, and not an initiator of carcinogenesis.

In animal studies, GSH was one of the earliest indicator of liver injury. Liver histopathology showed hydropic degeneration, swollen with cytoplasmic granules. Parenchyma and coagulate necrosis were also observed. Aberrant mitochondria and rough endoplasmic reticulum were also seen in substructural analysis of liver slices.

Control of water (13).

In 1972 before the algae toxins were positively identified in the ditch/pond water, we had proposed control of water qualities on the basis of data from epidemiological studies. We also suggested changing crop, and prevention of hepatitis, as a strategy for controlling PLC. In Qidong the local government began to pay more attention to the problem of contaminated water. Strong support was also provided by the population at large. During the years 1972-1980, more than 130 000 shallow wells in the county were filled in, and most of the inhabitants of Qidong were encouraged to dig deep wells (to a depth of more than 200 m). About 440 000 residents began drinking deep well water in the 1960s. Gastrointestinal tract diseases decreased significantly following improvement in the drinking water. Whether it will lead to a reduction in the incidence of PLC remains to be seen (14).

It was found that in Fusui County and later in many other counties the mortality of PLC was highest in those populations that drink pond water. A survey made in Nanning prefecture from 1969 to 1973 showed an annual mortality of 39.71/100 000 in population that rely on pond water. The mortality was reduced to 25.77 for those that use irrigation ditches, 19.56 for people who use water from the rivers. For residents that use water from the stream and deep wells, the mortalities were 18.74 and 12.17. Further analysis of the drinking water showed that the mortality of PLC varied with the degree of biologic pollution, such as bacterial count, excess nitrogen from nitrites and nitrates, presence of ammonium compounds, and oxygen consumption (15). In 1994 Fusui also changed their water sources from pond/ditch to deep well and tap water, affecting about 40% total population.

Discussion

During the past 48 years, scientists in China have used epidemiological methods to effect infectious disease elimination and chronic disease control. Where there have been noted success are cases in which strong associations were found between risk factors and the diseases in question. Examples are: Schistosomiasis control in suburb of Shanghai, the clams and hepatitis A explosion in Shanghai, decrease in cerebrovascular disease in the Luwan District of Shanghai. The current challenges, by contrast, involves low risks and weak associations, e.g., contaminated water and PLC, electric magnetic field, ionizing radiation and leukemia, micronutriants and

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digestive cancer, etc.

Our research on contaminated water and PLC provides a working model on dealing with infectious diseases that may have weak associations with alleged risk factors. Operationally, the implementation of the model involves the following steps: First, hypothesis must be formed based on assessment of real-life situations and distribution of disease. Second, it is essential to collect and check data from different authors, places, times; to use objective, laboratory, biomarkers, chemical methods. Third, meta-analysis should be used where possible. Collectively these methods would allow for development of better and more practical preventive measures, ultimately leading to improved health for the population.

Conclusions

(1) PLC is widely distributed in South-East China and is the number one cause of death in rural areas of China; (2) Epidemiological studies showed that contaminated water was an independent risk factor for PLC; (3) Contamination by algae toxins is an important risk factors for PLC; the odds ratio of contaminated water and PLC is 2.34 (95% CI, 1.09-5.02) and Population Attributable Risk is 30.39%; (4) The algae toxins, when combined with aflatoxins, is a strong promoter for development of PLC. Higher quantity of toxins can be detected from pond/ditch and small river, especially during June to September. Daily intake of toxin is about 255.6 ng/day; (5) In deep well water, algae toxins cannot be detected. Prevention strategy for PLC should include: controlling water qualities (using deep-well water for drinking), changing crop, and prevention of hepatitis.

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TABLE 1
Six case-control studies for PLC by Meta-analysis in China

Pond-ditch Water	Case	Controls	Odds Ratio (95% CI)	Heterogeneity	PAR % (95% CI)
Drinking	330	265	2.46	Q=9.10, df=5	30.39
Non-drinking	213	345	(1.69-3.59)	P>0.05	(23.30-37.47)
Well Water					
Drinking	176	165	0.75	Q=4.07, df=4	10.12
Non-drinking	300	240	(0.55-1.03)	P>0.05	
Tea					
Drinking	88	108	0.73	Q=2.49,df=2	9.98
Non-drinking	167	182	(0.45-1.19)	P>0.05	(3.56-17.23)

TABLE 2
Six case-control studies in Southern China by logistic regression

Pond-Ditch Water	Cases	Controls	OR	95% CI
Drinking	259	272	1.41	1.10-1.81
Non-Drinking	258	404		
	x^2 - Het = 5.83, P>0.05;			
	x^2 - Assoc = 7.96, P<0.01			
Period of Drinking (yr)				
0	254	383	1	
<36	87	98	1.33	0.93-1.91
36-	88	92	1.39	0.97-1.98
50-	88	88	1.49	1.04-2.13
	x^2 - Trend = 7.22, P<0.01			

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TABLE 3
The genotoxicities of MC extracted from Dianshan lake by Ames's test

Concentration μg/ml	TA100+S9	TA100-S9	TA98+S9	TA98-S9
0		117.7±2.1	26.7±1.5	24.0±2.0
0.5	122.7±3.8	119.3±4.2	19.7±1.2	27.3±3.5
1	129.0±1.0	127.0±3.1	26.7±2.1	47.0±8.7
2	135.7±3.1	135.0±2.5	42.7±7.4	52.7±3.2*
SA 0.1	-		-	-
2-AF 1.0	1035.3±55.2**	919.7±24.4**	877.3±26.0**	-
2,7-AF 10.0	-	-	-	933.3±34.2**

Wang HB, 1996

TABLE 4
The genotoxicities of MC extracted from Dianshan lake
Replicative DNA synthesis (RDS) & Unscheduled DNA synthesis (UDS)

Concentration μg/ml	RDS-CPM (M±S)	RDS-Ratio	RDS-CPM (M±S)	RDS-Ratio
Control	NS: 1947.0±223.2	1	DMSO: 952.7±74.1	1
Dianshan L				
1.25	2996.0±507.5	1.53	1637.3±314.2	1.72
12.5	3973.5±533.2	2.04*	1891.3±279.0	1.98
125	4416.7±743.0	2.27*	1882.7±273.3	1.97
Sod. Barbital				
100.00	5213.3±419.6	2.67*	-	-
Nitrogen				
Mustard 50	-	-		3.73*

Wang HB, 1996

TABLE 5
Two-stage transformation assay for MRT with SHE cells microcystin raw toxins

Initiator (μg/ml)	Promotor (μg/ml)	TF%
Dest aq	Dest aq	0.200
DMSO	DMSO	0.229
DMSO		0.341
MCA 0.5	DMSO	0.444
2		3.450
0.5	TPA 0.25	3.257
MRT 0.5		0.245
5		0.339
10		0.489
20		0.428
40		0.595
DMSO	MRT 0.50	0.272
	5	0.339
	10	0.522
MCA 0.5	MRT 0.50	0.615
	5	2.397
	10	3.488

Wang HB, 1996

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Development of Molecular Epidemiology in China

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Introduction

Molecular epidemiology is a new branch of epidemiology which utilizes molecular biological principles, methods and technologies to analyze problems in epidemiology, in order to gain insights on the molecular basis for disease occurrence in the population. Thus, contrary to classical epidemiology, in which broad observations are made by ecological, cohort, and case-control studies, the findings of which then generate leads on factors that effect changes on risks of diseases, molecular epidemiology represents a significant scientific improvement and evolution since it integrates and fine-tunes our understanding of the etiology and pathogenesis by directing our analysis of diseases at the level of nucleic acids and genes. In a broad sense, molecular biology may be used to further develop strategies for disease prevention and ultimately eradication.

Applications of molecular epidemiology are largely based on the following principles: Homeostatis in biological systems relies on timely expression of genetic information, leading to synthesis of proteins and enzymes. Although the genotypes of living organisms are determined by information in the nucleic acids, their phenotype activities are primarily effected by proteins. Disease occurrence, therefore, can arise from defects in phenotype expression. By gaining an understanding of the nature of these defects, it may be possible to have better control of diseases by developing mitigating factors to reduce the problems associated with the defects, by devising better prevention strategies and more effective treatment modalities.

Significance of molecular epidemiology

Traditionally, epidemiology is most frequently used to analyze risks associated with infectious diseases. Some commonly encountered problems include: dynamic and constant changes in the diseases themselves, complexity and multi-dimensional nature of risk factors, instability and/or redundancy of phenotypes, difficulty in differential diagnosis, and obstacles in standardization of exposure measurements and quantifications. By using assays that are targeted toward the genetic features of diseases, molecular epidemiological approaches circumvent some of these problems. Positive features associated with molecular epidemiology are: genetic transmission tends to be relatively more stable, expression of signals are more reliable, events leading to phenotype changes can more easily be traced.

Study of non-infectious diseases by epidemiological methods generally involve descriptive, analytical and laboratory studies. A common strategy is to identify risk factors using a case-control approach. Detailed analysis of various risk factors then provide clues concerning the pathogenesis of the diseases in question. Recent rapid advances made in molecular biological principles lead to major breakthroughs in the fundamental understanding of non-infectious diseases. For example, understanding of tumorigenesis and coronary heart diseases has benefited from discovery of oncogenes and anti-oncogenes. The discovery of proto-oncogenes has provided insights on mutational events leading to overexpression of proto-onocogenes, or to

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altered expression of proto-onocgens as oncogenes. Tumor suppressor genes were discovered on the basis of genes showing ability to revert malignant phenotype into normal phenotypes.

A brief introduction of the use of molecular epidemiology for infectious and non-infectious diseases in China is presented below.

Molecular epidemiologic studies of infectious diseases

Manifestation of infectious disease requires a source of infection, a means of transmission of the infectious agent, and a susceptible population. Each of these areas has now employed molecular epidemiological principles. However, due to costs involved in setting up laboratories, the application of these methods is not sufficiently common in different parts of China.

A. Identification and Establishment of the pathogenic agent. Poliomyelilis is an infectious disease known to have severe health impacts in children. It is therefore important to distinguish pathogenic strains from immunogenic strains of the pathogen. By combining PCR, RFLP and direct DNA sequnecing, it can be demonstrated that a pathogenic strain resulting from gene mutation was responsible for an outbreak of poliomyelitis in the inner region of China in 1990.

   Many pathogens cause diarrhea in humans. Molecular biology techniques were used to identify a new strain of E.coli, which differs from other E.coli strains in several ways: (i) notwithstanding the fact that it invades HEP-2 cells, the ipa B gene is lacking; (ii) although it induces aggregation of HEP-2 genes, it yields a negative result when hybridized against a E.coli probe; (iii) toxins produced by such a strain induces HEP-2 cell necrosis, and may be responsible for food poisoning.

B. Analysis of Means of transmission. The best studied case is one referred to a Yang Xiao-xia's Mysterious Disease which was eventually diagnosed as multi-bacterial synergistic gangrene. Using sera collected from normal individuals residing in the same county as the subject, and using four bacterial proteins isolated from the subject as antigens, western blot analysis ha shown that two of the antigens may be caused by the environment in which the subject resides. One possibly originates in the drinking water and may act as the primary pathogen leading to the infection.

   Lyme Disease is a tick-borne disease whose mode of transmission has been the subject of much study. The spirochette isolated from fetal liver was subsequently demonstrated to be genotypically related to B.garinii, suggesting that such a microorganism can be directly transmitted in animals.

C. Investigations of the natural host of the pathogen. In the case of spotted fever, molecular biological tools were used to analyze Dermacentor silvarum, Haemaphysalis concinna, Apodemus agrarius, Microtus fortis, leading to the demonstration that North-Asia tick-borne spotted fever probably originates in the upper Northeastern part of China.

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D. Analysis of characteristics and regularities in spread of infectious agents. Again molecular tools form the basis of multilocus enzyme analysis, wherein seven metabolic enzymes encoded by chromosomes were analyzed in an attempt to further understand typhoid fever.

E. Application in Disease Surveillance. Led to the demonstration of HIV-IC.

F. Application in preparation and development of vaccines.

Molecular epidemiology of noninfectious diseases

Many of the studies have focused on the involvement of the p53 gene in apoptosis and necrosis.

A. p53 gene. The major function of wild type p53 is to suppress cell proliferation and to induce apoptosis. Such a defense mechanism is especially important in DNA damage or in conditions of oxygen deprivation. The inhibition of cellular proliferation by p53 may be related to the suppression of c-myc gene expression. Mutated p53 has been shown to be associated with a variety of tumors and may also be correlated with the magnitude of the malignant state.

B. Antisense RNA.

C. Gene Defects

Conclusions

As a relatively new branch in the science of epidemiology, molecular epidemiology is probably rooted some five decades ago when the concept of molecular diseases was first introduced by Pauling. With new advances in technology, it can be anticipated that further strides will be made in our understanding of the molecular basis concerning the etiology and pathogenesis of disease occurrence and establishment in the foreseeable future.

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Applications of Cellular and Molecular Biological Markers in Public Health and Toxicological Research Investigations

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I. Introduction

Early detection, diagnosis and intervention are of fundamental theoretical and practical importance in preventive medicine. Applications of these principles require understanding and research of biomarkers, which, as was already pointed by scientists in the U.S. some ten years ago, are key to understanding the degree and magnitude of contact and exposure with toxicants, and health consequences related to such exposures. Three types of biomarkers, categorized as contact, effect, and susceptibility biomarkers, are considered to be central to furthering the knowledge and applications of preventive medicine.

The broad use of biomarkers in epidemiological studies in recent years has resulted in marked changes in the scope, dimension, and appreciation of disease occurrence, prevention, and control. Since the early 1990's, we have been developing technologies related to the use of cellular and molecular biomarkers in toxicological investigations. Specifically, our research efforts have focused on responses to exposure to toxicants, markers for effects related to contact and exposure to various types of toxicants, as well as appropriate markers for assessing susceptibility to toxicants. These research efforts have led to critical findings which give better handles on intervention measures. Some of these markers were used in early intervention trials Details of our studies follow.

II. Contact biomarkers

A. TTMA as a contact marker for exposure to benzene

Although benzene is widely used in industries for a variety of purposes, an accurate method for estimating the level of internal exposure to benzene is lacking. In recent years, because of advances made in our understanding of the metabolism of benzene, it has been proposed that a benzene metabolite, referred to as TTMA, could be used as a marker for exposure to benzene. Validation of the use of TTMA was recently established by our study checking urine TTMA in factory workers who had various levels of exposure to benzene. Results of this study show that urinary TTMA increased in proportion to the degree of contact and exposure with benzene. Specifically, urinary TTMA values in control, low, medium, and high benzene-exposed groups were 0.135±0.002, 0.199±0.10, 13.002±1.716, and 59.529±1.849 (in units of mg/g of creatine), respectively. These values were positively correlated with concentrations of benzene present in indoor air (correlation coefficient 0.93, $p<0.05$). Concentrations of TTMA may be determined using the following equation:

TTMA (mg/g) = 1.0 [benzene] (mg/m^3) - 0.2 hydroxylbenzene (phenol) (mg/m^3) - 0.8

It was also observed that exposure to phenol inhibited the formation of TTMA, as evidenced by the inverse relationship that existed between exposure to phenol and excretion of TTMA in the urine. Such a result could be explained by competition for metabolizing enzymes P450IIE1 and P450IIC11/6 common to the metabolism of benzene and phenol [4-7].

In sum, urinary TTMA is a reliable and sensitive biomarker for exposure to benzene.

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B. TTCA as a contact marker for exposure to carbon disulfide

Carbon disulfide is another commonly used organic solvent. Using high pressure chromatographic methods, Lu and coworkers reported that the urinary levels of TTCA may be considered to be appropriate biomarkers for contact exposure with carbon disulfide. The method used is capable of detecting 0.025 mg/l of TTCA. In a case control study, the following results were obtained: the control cases of 48 factory workers had a urinary level of 0.045 mg/g (range 0.005-0.140), whereas low and high exposed groups (involving a total of 60 factory workers) had TTCA of 0.248 (0.054-5.664) and 0.488 (0.066-3.646), respectively ($p<0.05$) [13]. Furthermore, exposed workers at a factory had high levels of urinary TTCA at the end of a working shift, compared to before the working shift [14]. Contact with carbon disulfide also led to substantial behavioral changes; an inverse correlation reportedly existed between TTCA levels and specific behavioral changes.

III. Effector biomarkers

A. Pre-tumorigenic markers.

1. Changes in glutathione S-transferase placental form, GST-P. In the aflatoxin B1-induced rat liver model in which specific focus was given to pre-tumorigenic changes, Ma and coworkers studied temporal changes in GST-P, using immunohistochemical techniques. It was reported that whereas GSP-T was below detection by week 5 after birth, immuno-positive cells can definitely be identified as early as week 4 following aflatoxin treatment. In contrast to these changes in GST-P, the traditional pre-tumorigenic marker for exposure to aflatoxin, GT-γ, did not begin to appear until week 6. Serum and tissue GST-P changes could also be used as pretumorigenic markers for liver cancer in humans.

2. Appearance of aberrant crypts. Intraperitoneal injection of dimethylhydrazine predictably results in colon cancer in rats and mice. Chen et al. studied changes in aberrant crypt formation and reported that the aberrant crypts can appear as early as week 9. Similar results were obtained irrespective of whether a single or multiple injections of DMH were administered. Oral administration of spirulina at 1500 mg/kg/day, given at the same time as DMH was administered, reduced the incidence of colon cancer. This was preceded by a significant reduction in aberrant crypts at weeks 9, 13 and 16, giving support to the idea that aberrant crypts could be used as pre-tumorigenic markers for colon cancer.

3. Changes in PCNA. Since uncontrolled cellular proliferation is considered to be a crucial step in malignancy, changes in PCNA have been studied as a possible pre-tumorigenic marker. Cheung et al. compared PCNA expression in liver of rats exposed to carbon tetrachloride, with or without the addition of vitamin E, zinc, selenium, manganese, and I132. A significant difference in the expression of PCNA was reported between control and carbon tetrachloride-treated animals. Certain protection in these animals was accorded by the simultaneous addition of vitamin E.

B. Effective markers of DNA damage

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1. DNA adduct formation. Chen et al. investigated formation of aflatoxin:DNA adducts. Specifically, AFB1-N7guanine and AFB1-FAP, as well as formation of benz[a]pyrene DNA adducts, i.e., BPDE and BPDE-N2dG, were evaluated as markers for DNA-specific changes that may accompany the administration of calorie restricted diets to animals. In one series of experiments, rats were given a 60% calorie restriction diet, without and without simultaneous supplementation with chromium. Chromium was found to suppress metabolic activation of AFB1 and reduce AFB1-N7guanine and AFB1-FAP by 40%, while at the same time increase glutathionine-AFB1 adduct formation by 50%. However, chromium administration was also shown to increase liver and lung BPDE-N2dG by 18% and 15%, respectively, showing that chromium has different effects on different carcinogenic substances

2. DNA:protein crosslinks, DPC. A relatively rapid, simple, and sensitive method for quantifying DPC was developed by Zhang et al. in 1994 using Chinese Hamster Ovary (CHO) cells. Validation of the method was established by studying effects of UV irradiation, K2CrO4, NiCl2, on formation of DPC in peripheral white blood cells, as compared to DPC formation in target tissues, and demonstrating that a good correlation existed between DPC of peripheral white blood and that of the target tissues. The method has since been extended to studies in humans. DPC values in normal individuals were determined to be 14466±396.5 cpm/μg (95% upper limt=2098.6). Exposure to chromium increased DPC [23]. In a separate study, the effects of carbon tetrachloride on DPC in peripheral white blood cells, was tested as a surrogate for damage to liver. DPC was shown to accurately reflect liver damage, suggesting that DPC is a suitable marker for DNA damage

3. Assessing DNA breaks by single cell electrophoresis. When DNA with single strand or double strand breaks are subjected to electrophoresis, the migration of DNA assumes a pattern characteristic of the appearance of comets. For this reason, this assay has been referred to as the "comet assay". Validation of this assay was established by comparing DNA breaks in peripheral blood lymphocytes of 52 workers exposed to benzene, as compared to 20 controls. The frequency of "comet" in the low and high exposed group was 7.5±6.62% and 16.8±9.6%, respectively, as compared to 3.0±2.7% in the control group ($p<0.01$ between cases and controls). Quantification of DNA breaks by using the "comet" assay requires that fresh blood samples be available, collected, and stored. The effects of metals on induction of DNA breaks were recently investigated. Ni3S2, with an active dosage of 2.5-10 $\mu g/cm^2$, was found to be more effective than NiCl2, whose effective dosage was 500-2000 $\mu g/cm^2$.

4. Oxidative DNA damage and 8-hydroxy-2-deoxyguanosine formation. DNA damage can result oxidative stress, promoting the formation of 8-hydroxy-2-deoxyguanosine which, if not repaired timely and properly, can lead to transitional mutations. The levels of 8-hydroxy-2-deoxyguanosine in the kidney were found to reflect damage to the kidney that results from exposure to renal toxins. Furthermore, alterations in serum 8-hydroxuguanosine were reportedly correlated with exposure to benzene in both male and female workers.

5. Changes in PARP. Poly(ADP-ribose) polyemerase catalyzes DNA-dependent ligation of DNA ends. Activity of PARP may reflect the extent of DNA damage as well as the capacity for repairing the damaged DNA. Zhang et al. showed that PARP was correlated with the dose of Ni3S2 used to induce DNA damage (r=0.97). PARP changes also matched with results of the "comet" assay (r-0.98)

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C. Oxidative damage in proteins. Enzyme activities, as well as structural and cellular functions of proteins can be adversely affected by oxidative damages induced in proteins. Xhang et al. observed that when BSA was incubated with Cu, Fe, Cr, Ni, Co, Cd, and Pb, oxidative damage in BSA occurred with the first 5 metals.

D. Effector biomarkers for damages to chromosomes

1. Oral exforiative epithelial micronucleus OEFMN formation. Although appearance of micronucleus in peripheral blood lymphocytes has been used extensively to score damage on chromosomal DNA, blood samples can only be obtained by using an invasive procedure, and as such is potentially a barrier to investigation. Since buccal cells are more easily obtained, it may be offered as an alternate to blood cells. Validation of buccal cells in studies of damage to chromosomal DNA was recently confirmed in an investigation that compared OEEMN of 55 workers exposed to benzene (levels of exposure range from 40.8-792 $mg/^3$), with those of controls. The values of OEEMN was 9 (0-47%) for the exposed group and 1.5% for the controls (0-10, $p<0.001$). Interestingly, in the same study the white blood cell count of the exposed workers were found to be within the normal values, suggesting that OEEMN of buccal cells is a more sensitive assay for assessing damage to chromosomal DNA. In a separate study, OEEMN was also assessed in nurses with long term exposure to chemotherapeutic agents. The OEEMN was found to be 6.23±3.26%, as compared to the OEEMN of 0.97±0.76% for controls ($p<0.05$). These results were in close agreement with appearance of micronuclei in peripheral blood lymphocytes (5.10±1.85% for the exposed group versus 1.75±1.56% for controls, $p<0.01$). These results strongly support the validity of the OEEMN assay. The possibility that genetic damage may result from prolonged exposure to chemotherapeutic agents is also raised by these studies.

2. Damage to chromosomal DNA in spermatocytes and assessment of aneuploidy.

E. Expression of the tumor suppressor gene p53. Whereas expression of the wild type p53 is normally below detection levels, based on immunochemical assays, mutation of the p53 gene has been shown to significantly increase p53 expression, making its detection possible. In a recent study, p53 expression in 3 groups of subjects were compared. The first group consisted of 28 subjects residing in heavily polluted areas. A second group involved 18 subjects from less heavily polluted areas, and a third group was represented by 16 cancer patients. Expression of the p53 was measured in peripheral blood lymphocytes. Results show that the p53 expression of the cancer patients, and subjects residing in polluted areas, and their respective controls were 222.75 (119.99-431.98), 60.04 (20.00-124.01) and 15.95 (8.00-28.06), respectively. Positive results were scored in 86%, 30.3%, and 11.1% of the lymphoid cells.

F. Markers for neuroendocrine toxins.

IV. Susceptibility markers

A. Chromosomal breakage in peripheral blood lymphocytes.

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B. GST M1 polymorphism.

V. Conclusions

Much effort has been spent in recent years to apply biomarkers use in epidemiological investigations. Since the early 1990s, we have been interested in developing new and novel cellular and molecular biomarkers, in an attempt to establish the degree of contact with toxic substances, to demonstrate early contact toxic responses, and organic sensitivities resulting from exposure to toxic substances.

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Diet and Antioxidant - a Nutritional Intervention Study

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Abstract

It has been implicated that high vegetable intake is associated with a decreased risk for various forms of cancer in epidemiological studies. A major defense system against cancer has shown to be antioxidants. Glutathione S-transferases (GSTs), one of the major defense systems against oxidative damage, can be induced by antioxidant and oxidative stress through antioxidant responsive elements. In a pilot intervention study, eight subjects were given an addition of vegetables to their normal diet. Serum retinol and a-tocopherol were determined by HPLC and the gene expression of GSTπ in lymphocytes was measured by reverse transcription - polymerase chain reaction (RT-PCR) techniques. The results showed that there was no significant difference in the levels of serum retinol and a-tocopherol before and after the addition of vegetables. GSTπ mRNA levels in lymphocytes were higher in four out of five subjects after addition of vegetables. The results suggested that it might be other antioxidants than vitamin A and E in the vegetables that induced the gene transcription of GSTπ.

Introduction

Diet has been implicated in the etiology of 10-70% of human cancer (Doll and Peto, 1981). Several studies suggest that antioxidants are important in the defense against environmental carcinogens (Frei et al 1988, Bailey and Williams 1993). As several food items, notably vegetables, contain antioxidants, a low intake of these would increase the risk for cancer. Numerous epidemiological data demonstrate a relation between the risk for cancer and the consumption of vegetables (for a review see Ziegler et al 1996). It is generally agreed that the consumption of vegetables decreases the risk, particularly for lung cancer (Byers et al 1984, LeMarchand et al 1989, Jain et al 1990, block et al 1992, Steinmetz et al 1993, Axelsson et al 1996, Rylander et al 1996, Serdula, 1996). The results from a recent study in Sweden is shown in Figure 1.

The Figure 1 illustrates that the risk for lung cancer was about half among persons with a frequent consumption of vegetables.

An important part of the antioxidant defense system is glutathione S-transferase (GSTs), a family of isozymes divided into three main classes, π, a and μ (Mannervik et al 1985). GSTs catalyze the reaction of a wide variety of electrophiles with glutathion (GSH). Since most of the reactive forms of chemical carcinogens are electrophiles, GSTs may contribute considerably to carcinogen inactivation (Coles 1990). Enhancement of this enzyme system coukd potentially increase the capacity to withstand the daily burden of carcinogens and may thus reduce the risk of developing cancer (Carr 1985). It has been suggested that antioxidants might have a protective effect by activating genes of importance for the defense system against oxidative stress through

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specific oxidative regulatory elements (Rushnore et al, 1990, Paulson et al 1990). GSTs are known to carry the antioxidant responsive elements in upstream of the 5`-flanking region (Truyen Nguyen et al 1994).

The influence of diet on GSTs enzyme activity and protein levels has previously been investigated in plasma, lymphocytes and intestine. Consumption of Brussels sprouts was found to increase the level of GST a in serum and GST α and π iin rectal mucosa (Wim An et al 1995). In several studies the analysis of lymphocyte gene expression has been shown to miooro the hepatic level of gene expression. The expression of CYP2E1 and CYP2D6 in lymphocytes has been shown to reflect the hepatic gene expression of the same genes (Raucy et al 1995, Carcillo et al 1996). It is thus possible to analyze the status of GSTs gene at the mRNA level using reverse transcription-polymerase chain reaction (RT-PCR) in lymphocytes.

To further evaluate the possible role of vegetables, an intervention study was performed, where test persons received an addition of vegetables to their normal diet and measurements of GSTs gene expression at mRNA level were made before and three weeks after the intervention.

Materials and methods

Subjects

For the intervention eight never smoking healthy males, aged 20-30 years were recruited by advertising among university students. The subjects were interviewed regarding normal dietary habits and a 24- hour recall was made. Their body mass and daily caloric intake were determined.

Intervention

At the beginning of the study, blood samples were taken. Thereafter, the subjects received 300g mixed vegetables / day to be eaten with their usual diet for three weeks. Blood samples were drawn at the end of study. This intervention study was approved by the Ethical Committee at the Medical Faculty of Gothenburg.

Determination of retinol and a-tocopherol in plasma

Six ml of whole blood were collected in a gel-barrier EDTA tube (kept away from natural illumination) and centrifuged at 4000 rpm for 10 min at room temperature. The supernatant was transferred to another tube and retinol and a-tocopherol were determined by high pressure liquid chromatography (George L. C. et al, 1983).

Preparation of lymphocytes

Eight ml of whole blood were collected in a Vacutainer-CPT tube (Becton Dickinson Vacutainer Systems, N. J.). Within one hour of collection this sample was centrifuged for 20 min at 1500 g at room temperature. The lymphocyte layer was transfered to another tube.

Isolation of RNA from lymphocytes

Total RNA were isolated by the rapid guanidium thiocyanate/phenol/chloroform single-step extraction method (Trizol LS Reagent, Life Technologies, Gaithersburg, Maryland). The

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purity and quantity of RNA was determined spectrophotometrically (Perkin-Elemer Lambda 5UV/Vis Spectrophotometer). The quality of RNA was determined on agarose/formaldehyde gel. Samples with bad quality of RNA were not included.

Reverse transcription, PCR amplification (RT-PCR)

Total RNA was reversed transcripted by Advantage RT-for-PCR kit (Clonetech, East Meadow Circle, CA). The specific primers for GSTπ were corresponding to exon 4 and 7. Exon 4, 190-209: 5'-TAC CAG TCC AAT ACC ATC C-3'. Exon 7, 611-630: 5'-CTG TTT CCC GTT GCC ATT G-3'. The cDNA was denatured at 94°C for 40 sec., annealed at 58°C for 45 sec. And extended at 72°C for 90 sec., using 1.5 mM $MgCl_2$. The cycles of amplification were 30. For each amplification reaction, the amplification of beta-actin as internal standard was made.

Results

Determination of retinol and a-tocopherol in serum

Serum retinol and a-tocopherol levels before and after the addition of vegetables are reported in table 1. There are no significant differences before after the addition of vegetables to the diet.

GSTπ gene expression in lymphocytes

In subject No. 1, 5, 6, the RNA quality was not acceptable. The results from the remaining five are shown in table 2. GSTπ mRNA levels was higher in four out of five subjects. In subjects No. 2, GSTπ mRNA level varied from low to high expression after the addition of vegetables. In subject No. 3, 4, 7, 8, mRNA could only be detected after the addition of vegetables.

Comments

The study was of a pilot nature and performed mainly to establish methods and the experimental protocol. The number of subjects was small and the results must be interpreted with care. The addition of vegetable to the normal diet was well tolerated and did not lead to any change in the basic diet (data not reported).

The addition of vegetables to the diet did not cause any increase in the blood levels of retinol or a-tocopherol. The transcription of GSTπ gene was however increased. This might indicate that the protective effects of vegetables is not necessarily ascribed to one or two micronutrients like vitamin A and E. Some other antioxidants in the vegetables might activate the antioxidant responsive element of the 5'-regulatory region of the GSTπ gene and induce the gene transcription. It has been reported that sulforaphane, an aliphatic isothiocyanate found in cruciferous vegetables and its analogue-sulforamate, could interact with the antioxidant responsive element and significantly induce mouse mammary GSTs activity. These compounds were identified as potent inhibitors of preneoplastic lesion formation in carcinogen-treated mouse mammary glands in organ culture (Gerhauser C. et al 1997).

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TABLE 1

Plasma retinol and a-tocopherol levels before and after addition of vegetables in the diet

Subject	Retinol (mmol/l)		Tocopherol (mmol/l)	
No.	before	after	before	after
1	2.0	2.0	11.8	11.7
2	2.9	3.0	21.1	23.8
3	2.0	2.0	20.8	18.1
4	2.5	2.4	17.5	19.4
5	1.7	1.8	12.7	12.6
6	2.1	2.2	17.2	20.2
7	1.9	2.4	18.1	19.0
8	2.6	2.6	13.0	15.0
mean±SD	2.2±0.4	2.3±0.4	16.5±3.6	17.5±4.1

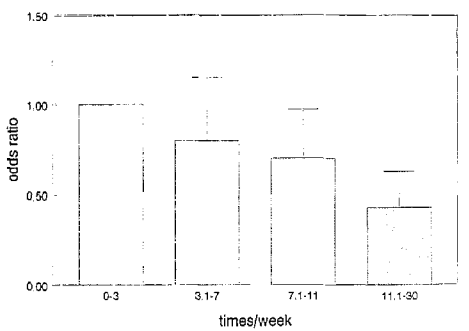
TABLE 2

The GSTπ mRNA in lymphocytes before and after addition to vegetables in the diet (ND: not detected)

Subject No.	GSTπ mRNA	
	before	after
2	+	++
3	ND	ND
4	ND	+
7	ND	+
8	ND	+

FIGURE 1

Odds rations for lung cancer risk and vegetable intake among 536 male and female lung cancer cases and 916 controls. The consumption of carrots, tomatoes, lettuce, cabbage and green/red pepper is expressed as times/week. Adjusted for age and smoking habits.



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Monitoring Personal Exposures to Environmental Air Pollutants

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Abstract

The fields of environmental epidemiology and analytical chemistry should work more closely together and, with careful planning, could result in the two discrete disciplines complementing each other in a most positive way. Some of the methods for sampling air and its subsequent analysis have been described and analytical measurements have been compared with subjective assessments. Some real world exposure values for respirable suspended particles and environmental tobacco smoke in Hong Kong and Beijing have been contrasted with those for Barcelona in Europe. Time weighted average concentrations were discussed and cumulative frequency distributions compared between cities.

1. Introduction

Most epidemiological studies are based on observational information and epidemiologists often do not have the benefit of measurable precision when considering and comparing exposure groups. Results are therefore nearly always skewed in some way with information bias being one of the major sources of error introduction (1).

When using questionnaire data, a subject's ability to accurately recall information is questionable, as is the use of measuring equipment without strict calibration protocols. Both are major considerations if the integrity of the data is to remain intact. The introduction of such bias cannot be eliminated by conventional data analysis and the magnitude of the bias can be very significant. Therefore because of the inherent weaknesses associated with being solely reliant on questionnaire data, exposure or dose measurements should be a major consideration when designing epidemiological studies. Because these studies are planned to assimilate data over a period of several years it is also important to consider performing measurements of exposure on a number of occasions during the study period.

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2. Epidemiology

It has been said that epidemiologists "watch the world as it is and accept the interplay of numerous factors influencing phenomena they are trying to study" (2). Chemists on the other hand try to measure everything relevant to their research and attempt to understand phenomena in the simplest way by monitoring systems that are totally isolated from external influences. By joining forces, large scale epidemiological studies have benefited from data provided by chemists when assessing exposure levels to harmful pollutants both in the environment and in human tissue.

As a health science, epidemiology is the study of the distribution of disease in populations and factors, including life style information, associated with the distribution. Epidemiology therefore focuses on groups of people and not on individuals. Characterisation of disease distribution can be by person, place and time.

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Risk factors increase the probability of disease. Epidemiologists look for and identify associations between risk factors and disease and assess these associations for signs of cause. The time from exposure to onset of disease must be taken into consideration when assessing the cause. A link between any risk factor and disease is shown by an increase in risk relative to those groups without the risk factor present (Relative risk) or by the proportion of disease associated with a given risk factor (Attributable risk).

The major independent variable for the determination of relative risk is exposure and, to be of any value, environmental epidemiology studies depend very much on the integrity of the exposure calculations.

General consideration must be given to the following problems associated with exposure estimation:

2.1 Technical measurement

- expense
- lack of knowledge of environmental behaviour

2.2 Entry into the body

- several routes to consider
  - inhalation (very important)
  - ingestion
  - skin absorption

2.3 Source of exposure

These may be multiple sources e.g.

- benzene from petroleum sources (outside)
- benzene from smoking (inside)
- lifestyle will therefore be important

2.4 Population size and time frame

- large numbers of people for long periods of time
- median values or geometric means etc.

Presently there is very little information available on the relative importance of the different types of summary statistics available for exposure estimation.

3. Analytical chemistry

Technological improvements in detection systems used for the analysis of pollutants in our environment enables chemists to measure smaller and smaller quantities. These improvements in detection limits have shown that some compounds are ubiquitous having been measured in our food, water, air and our tissues. So today, although we have a far more complete picture of the many trace contaminants and pollutants associated with everyday life, we have not improved our understanding of the significance of these trace level compounds. The health effects of these trace pollutants involves the interpretation of risk assessment derived from well designed epidemiological studies.

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4. Air Sampling

Almost 200 air pollutants are currently causing concern in the USA. We have an endless choice of what we drink and also what we eat but when it comes to the air we breathe we have no choice.

4.1 Problems associated with air sampling

- unique medium
- samples can differ significantly due to wind changes
- emission sources and their timings
- analytes can be reactive and at very low concentrations
- can be distributed between two or more phases e.g. gases, solids, liquids
- low concentrations complicate the analysis of samples e.g. large volumes may have to be collected increasing the presence of interferents during analysis.

4.2 Representative Sampling

Large variations in analyte concentrations over relatively short time periods are common with air samples. Consequently this may lead to unrepresentative sampling.
Important considerations for obtaining representative air samples include:

- The efficiently of the collection apparatus
- Integrity of the entry and removal of the sample from the apparatus
- The sampling site or location
- The collection period (time)
- Use of personal monitors versus ambient fixed monitors

The most widely used procedure for sampling ambient air for volatile compounds is to pass measured volumes of air (typically measured in litres) through solid material which adsorbs the compounds of interest. Desorption takes place prior to analysis.

For less volatile compounds, that may be phase distributed, particle filters are used and subsequently extracted prior to analysis. Personal sampling pumps are a reliable means of collecting air samples. They draw air through sampling devices such as resin tubes, filters and impingers and have adjustable flow rates.

Non-volatile compounds such as dusts or elemental carbon etc. with high molecular weights are sampled in the same way. PM_{10} samplers or similar collect particles with a mass median diameter of 10 microns from ambient air. Particles of this size represent the respirable fraction and therefore are of major significance.

5. Subjective assessments of exposures

During the course of the last two years twelve major cities have been investigated by this author and research co-workers for respirable suspended particles (RSP) and environmental tobacco smoke (ETS) exposure in nonsmoking housewives and nonsmoking office workers. On average 200 volunteers, representative of each city, wore a personal monitor over a 24 hour period.

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